SAREPTA THERAPEUTICS

OUR VISION FOR THE FUTURE OF

Precision Genetic Medicine

SAREPTA THERAPEUTICS 2018 R&D DAY

FORWARD-LOOKING STATEMENTS

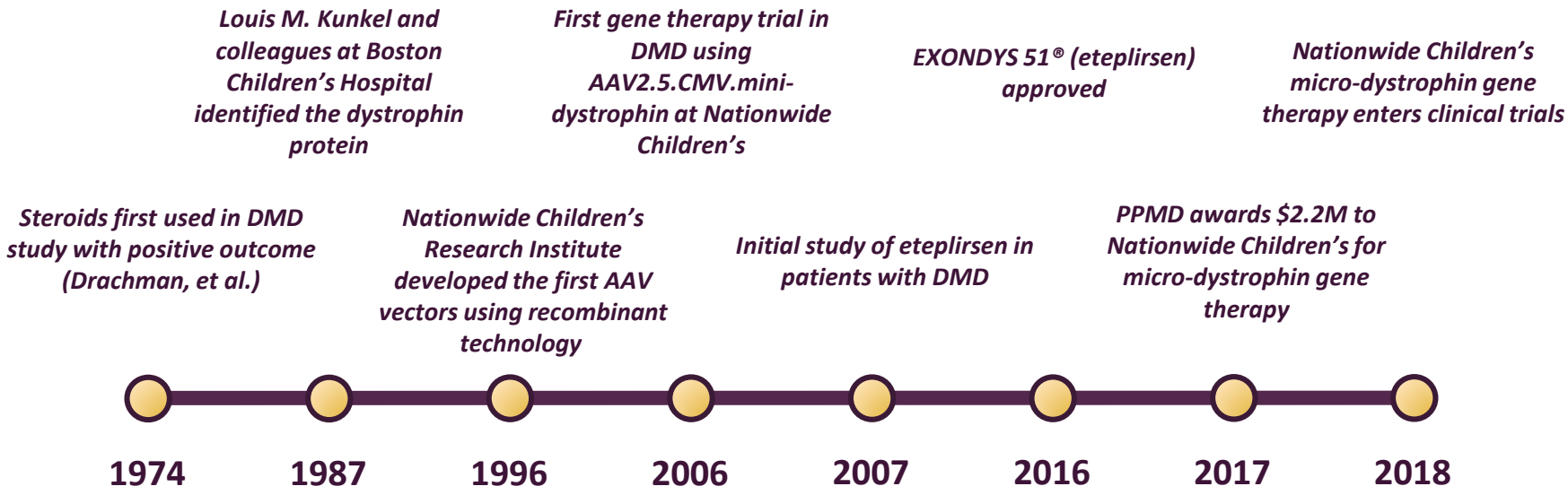
The R&D Day presentations contain "forward-looking statements." Any statements that are not statements of historical fact may be deemed to be forward-looking statements. Words such as “believe,” “anticipate,” “plan,” “expect,” “will,” “may,” “intend,” “prepare,” “look,” “potential,” “possible” and similar expressions are intended to identify forward-looking statements. These forward-looking statements include statements relating to Sarepta’s strategic approach to treating fatal rare diseases and its building blocks for its strategy; Sarepta’s pipeline and the potential benefits of Sarepta’s product candidates and technologies, including in collaboration with strategic partners, such as PPMO’s potential to affect exon skipping and its applicability across many diseases, including those in central nervous system, the potential of genome editing to correct muscle stem cells and restore functional dystrophin, the potential of a single genome editing strategy to apply to 40-63% of DMD patients, GALGT2’s potential to treat almost all patients with dystrophin deficiencies irrespective of mutation type or location, MHCK& promoter’s potential to enable robust expression in heart and skeletal muscle, AAVrh74’s potential to provide broad distribution to all muscle groups including the heart and diaphragm, the expectation that rh74 AAV transduced muscle fibers be protected indefinitely, rh74 AAV’s superior skeletal muscle transduction and its ability to support single-administration hypothesis, MHCK7’s potential ability to optimize cardiac expression (LGMD2E and LGMD2B) and tMCK’s potential ability to minimize cardiac expression (LGMD2D); expected milestones and timelines, including filing an IND for SRP-50g in Q4 2018, filing an IND for follow-on PPMO compounds in 2019, initiating a Phase 1/2a study for MYO-101 (LGMD2E) in Q3 2018 and having preliminary results in Q1 2019, filing an IND amendment for MYO-102 (LGMD2D), having a pre-IND meeting in mid-2018 re MYO-103 and filing an IND amendment for GALGT2; the expected LGMDs patient population and LGMDs representing a large unmet need; expected studies design; Myonexus LGMD programs targeting approximately 70% of the LGMD population with current pipeline; and shared design principles increasing efficiency between the LGMD programs.

These forward-looking statements involve risks and uncertainties, many of which are beyond Sarepta’s control. Actual results could materially differ from those stated or implied by these forward-looking statements as a result of such risks and uncertainties. Known risk factors include the following: success in preclinical testing and early clinical trials, especially if based on a small patient sample, does not ensure that later clinical trials will be successful, and initial results from a clinical trial do not necessarily predict final results; Sarepta’s ongoing research and development efforts may not result in any viable treatments suitable for clinical research or commercialization due to a variety of reasons, some of which may be outside of Sarepta’s control, including the results of future research may not be consistent with past positive results or may fail to meet regulatory approval requirements for the safety and efficacy of product candidates, possible limitations of Company financial and other resources, manufacturing limitations that may not be anticipated or resolved for in a timely manner, and regulatory, court or agency decisions, such as decisions by the United States Patent and Trademark Office with respect to patents that cover our product candidates; and even if Sarepta’s programs result in new commercialized products, Sarepta may not achieve any significant revenues from the sale of such products; if the actual number of patients suffering from DMD and LGMD is smaller than estimated, Sarepta’s revenue and ability to achieve profitability may be adversely affected; and those risks identified under the heading “Risk Factors” in Sarepta’s most recent Annual Report on Form 10-K for the year ended December 31, 2017 or most recently filed Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) as well as other SEC filings made by the Company which you are encouraged to review.

Any of the foregoing risks could materially and adversely affect the Company’s business, results of operations and the trading price of Sarepta’s common stock. You should not place undue reliance on forward-looking statements. Sarepta does not undertake any obligation to publicly update its forward-looking statements based on events or circumstances after the date hereof, except to the extent required by applicable law or SEC rules.

Parent Project Muscular Dystrophy Video

A BRIEF HISTORY OF DUCHENNE MUSCULAR DYSTOPHY (DMD) AND GENE THERAPY



THERE HAVE BEEN MANY STRIVING TO BRING A BETTER LIFE TO THOSE WITH DMD

PATIENTS, CAREGIVERS AND ADVOCATES

CLINICIANS AND SCIENTISTS

THE BIOTECH ECOSYSTEM

OUR PURPOSE (Patient with DMD video)

OUR STRATEGIC APPROACH TO TREATING FATAL RARE DISEASES

RNA-TARGETED THERAPIES PMO/PPMO

OUR STRATEGIC APPROACH TO TREATING FATAL RARE DISEASES

GENE THERAPY

GALGT2 and Micro-dystrophin

RNA-TARGETED THERAPIES

PMO/PPMO

OUR STRATEGIC APPROACH TO TREATING FATAL RARE DISEASES

GENE EDITING — CRISPR/Cas9

GENE THERAPY — GALGT2 and Micro-dystrophin

RNA-TARGETED THERAPIES — PMO/PPMO

OUR STRATEGIC APPROACH TO TREATING FATAL RARE DISEASES

OTHER THERAPEUTIC AREAS

Limb-Girdle Muscular Dystrophy/Myonexus

GENE EDITING

CRISPR/Cas9

GENE THERAPY

GALGT2 and Micro-dystrophin

RNA-TARGETED THERAPIES

PMO/PPMO

THE BUILDING BLOCKS FOR OUR STRATEGY

TRANSFORMING PIPELINE AND ACCELERATING R&D EFFORTS

RAISING RESOURCES TO FUEL FUTURE GROWTH

BOLSTERING INFRASTRUCTURE AND MANUFACTURING CAPABILITIES

ATTRACTING AND RETAINING TOP TALENT

DR. LOUISE RODINO-KLAPAC: HEAD OF OUR GENE THERAPY DIVISION

- Joined Sarepta Therapeutics in June 2018 from Nationwide Children's Hospital where she was head of the laboratory for gene therapy research for the treatment of muscular dystrophies
- Previously served as an Associate Professor of the Department of Pediatrics at Ohio State University College of Medicine
- Co-founded Myonexus Therapeutics, Inc., a clinical-stage gene therapy biotech company focused on treatment of limb-girdle muscular dystrophy
- Was the recipient of numerous awards, including the Forty Under 40 Award by Columbus Business First, and the Department of Pediatrics Outstanding Junior Faculty Award for Innovation
- Authored numerous publications, including papers published in *The New England Journal of Medicine*, *Annals of Neurology*, and *Pediatric Neurology*
- Earned her bachelor's degree in biology from Kings College, and a Ph.D. in molecular genetics from The Ohio State University

DR. GILMORE O'NEILL: CHIEF MEDICAL OFFICER

- Joined Sarepta Therapeutics in June 2018 from Biogen where he was responsible late-stage clinical development
- Oversaw development programs for Alzheimer's disease, movement disorders, acute neurology, multiple sclerosis, pain, neuromuscular disease, gene and cell therapy, and rare diseases
- Played a leadership role in seeking, receiving and maintaining global marketing approvals for Tecfidera®, Zinbryta®, Plegridy® and Spinraza®
- Is a member of the American Academy of Neurology and a board-certified neurologist (ABPN)
- Previously served as director of the leukodystrophy service and chief resident of neurology at Massachusetts General Hospital
- Earned a Bachelor of Medicine degree at University College Dublin and a Master of Medical Sciences degree from Harvard University

OUR VISION FOR THE FUTURE OF

Precision Genetic Medicine

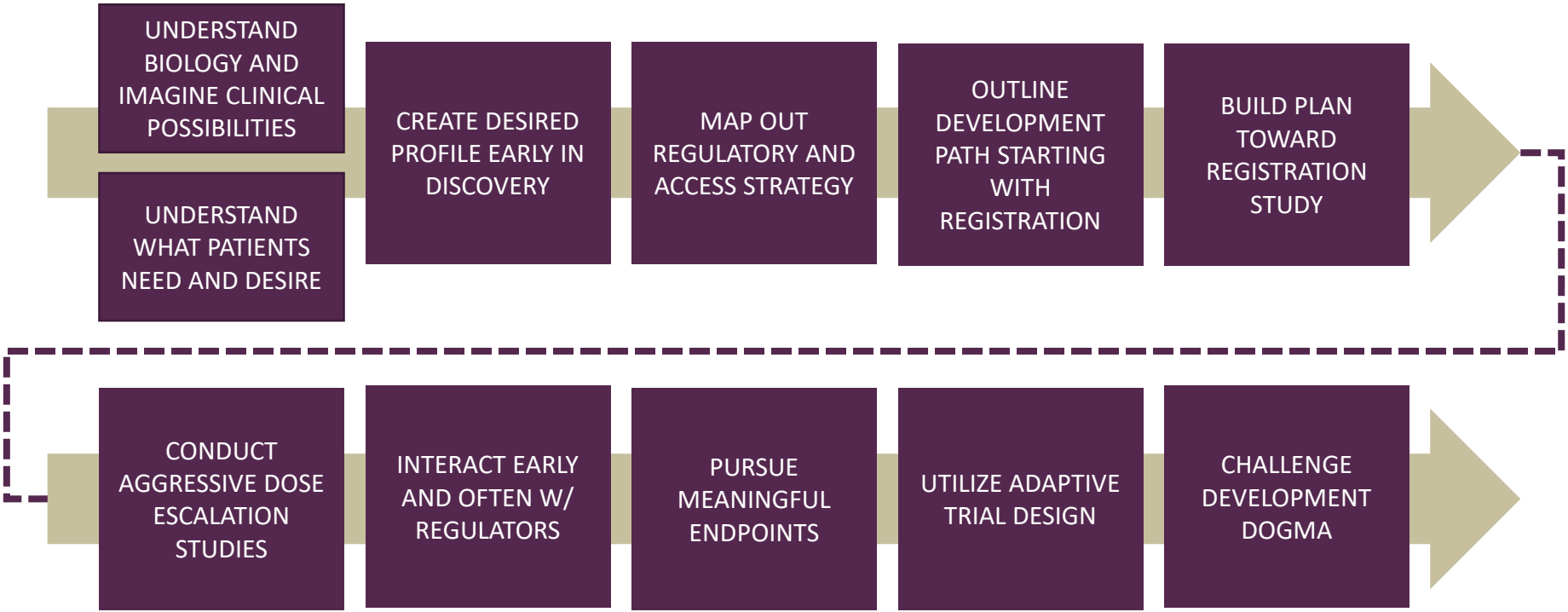
SAREPTA THERAPEUTICS, INC 2018 R&D DAY

Clinical Development Philosophy and Approach

Gilmore O'Neill, M.B., M.M.Sc.
Chief Medical Officer
Sarepta Therapeutics

SAREPTA THERAPEUTICS

PHILOSOPHICAL APPROACH TO CLINICAL DEVELOPMENT



Put patients first; deliver what patients need; use the best development and regulatory science to do this

LEARNING FROM PREVIOUS EXPERIENCES

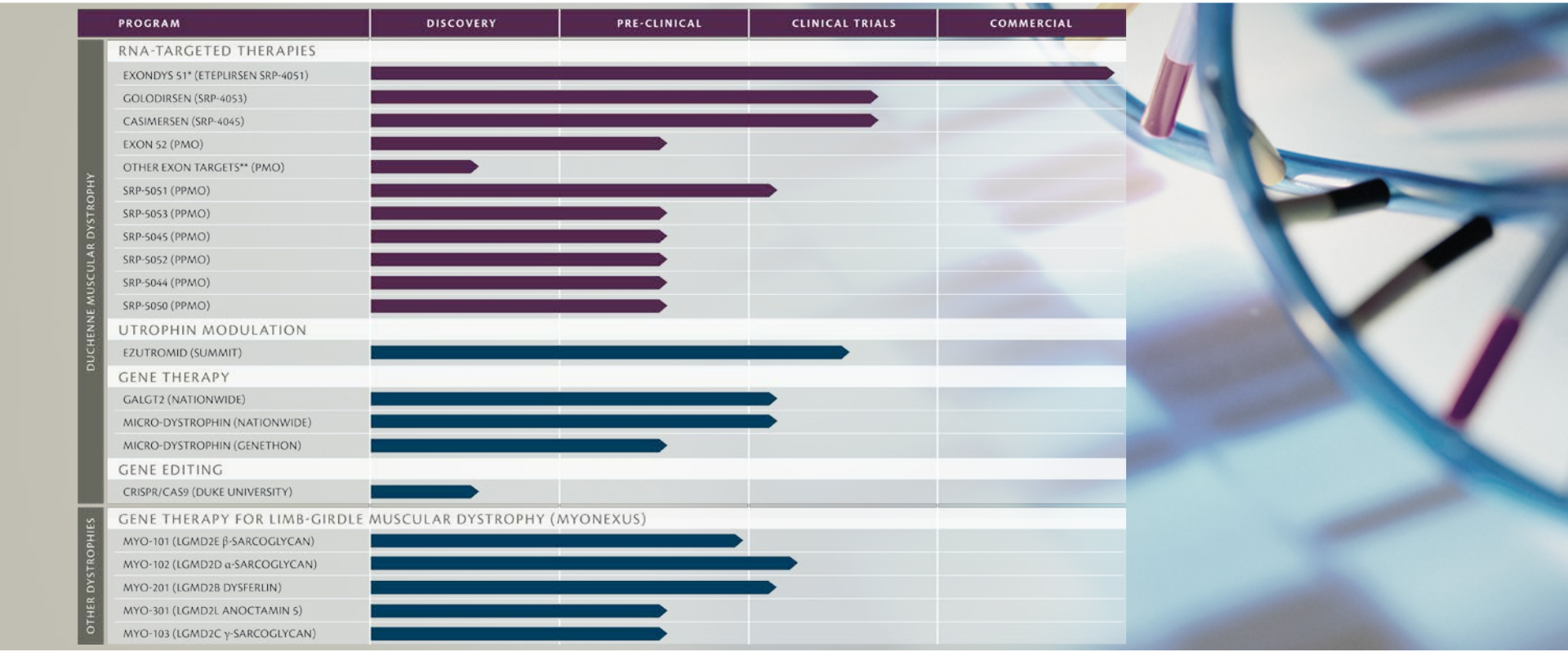
WHAT WORKS

- Always focusing on patients—welfare and needs
- Fully understanding the biology to control confounding variables
- Designing the perfect set of clinical studies, then adjusting for the real world
- Challenging dogma
- Remaining humble—biology and disease are complicated foes
- Collaborating closely with regulatory agencies

WHAT DOESN'T

- Not talking to the patients who we want to help
- Ignoring biology
- Ignoring pharmacology
- Ignoring regulatory agencies
- Thinking that you have all of the answers
- Treating other developers as opposition
  - We share the same goal, can learn from one another, and create opportunities for one another

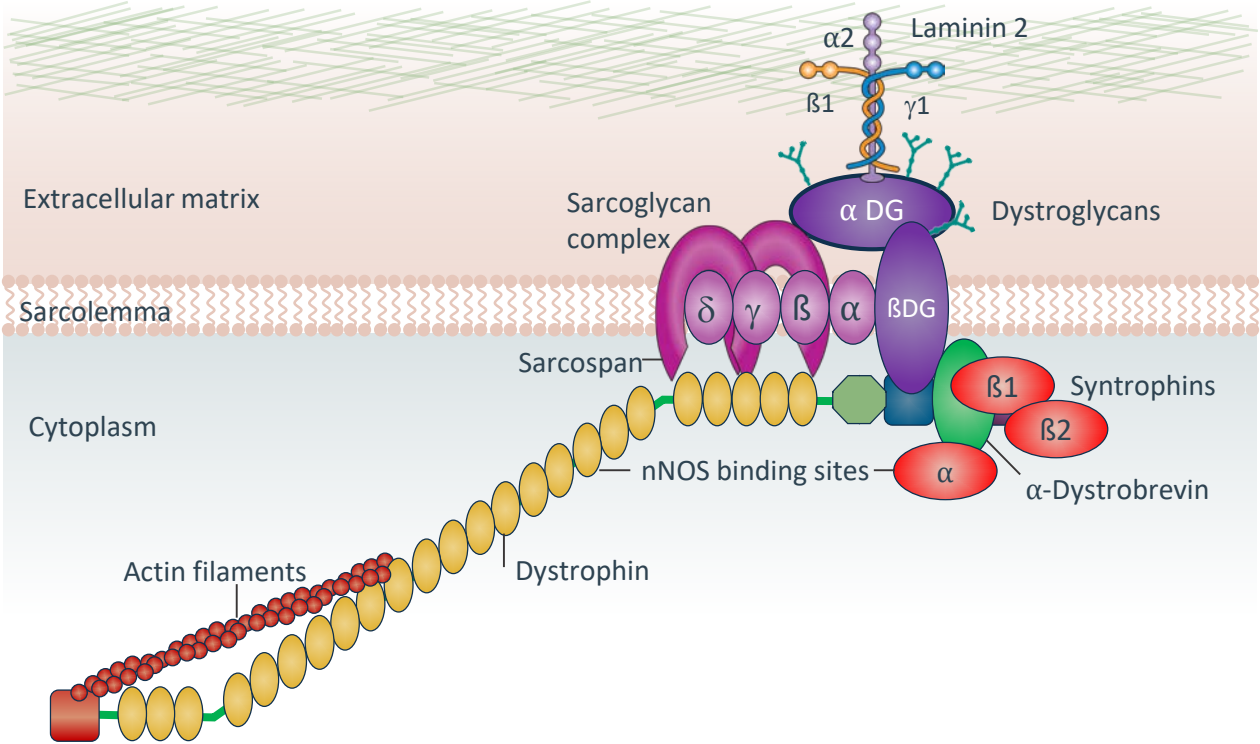
ADVANCING ONE OF THE MOST ROBUST PRECISION GENETIC MEDICINE PIPELINES IN THE INDUSTRY



Internal
External Collaborations

*EXONDYS 51 received accelerated approval in the U.S., confirmatory studies required
**Other exon targets in development: 8, 35, 43, 44, 50, and 55

OUR CORE EXPERTISE IS TARGETING THE DYSTROPHIN-ASSOCIATED PROTEIN COMPLEX TO TREAT MUSCULAR DYSTROPHIES



nNOS, neuronal nitric oxide synthase.

Image adapted from Fairclough RJ, et al. *Nat Rev Genet*. 2013;14(6):373-378.

OUR CORE EXPERTISE IS TARGETING THE DYSTROPHIN-ASSOCIATED PROTEIN COMPLEX TO TREAT MUSCULAR DYSTROPHIES

PRESENTER

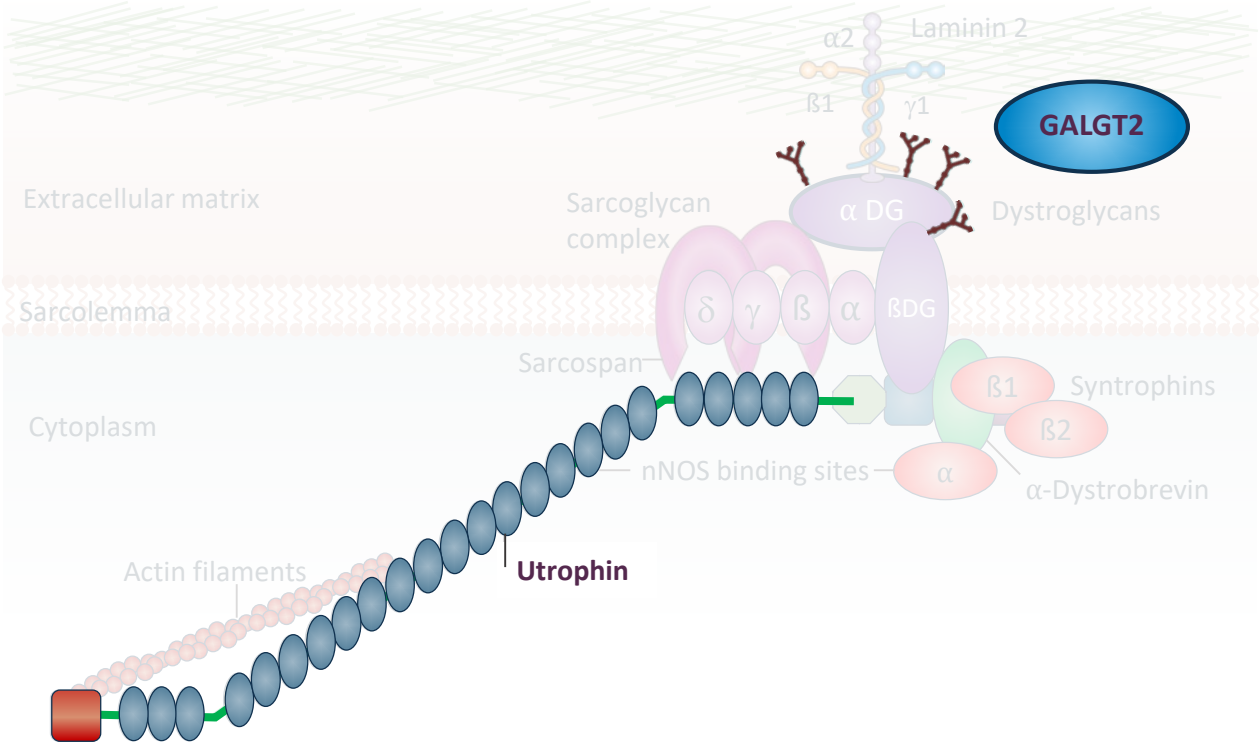
Kevin M. Flanigan, M.D.

APPROACH

GALGT2 gene therapy

DISEASES

- **Duchenne muscular dystrophy**



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PRESENTER

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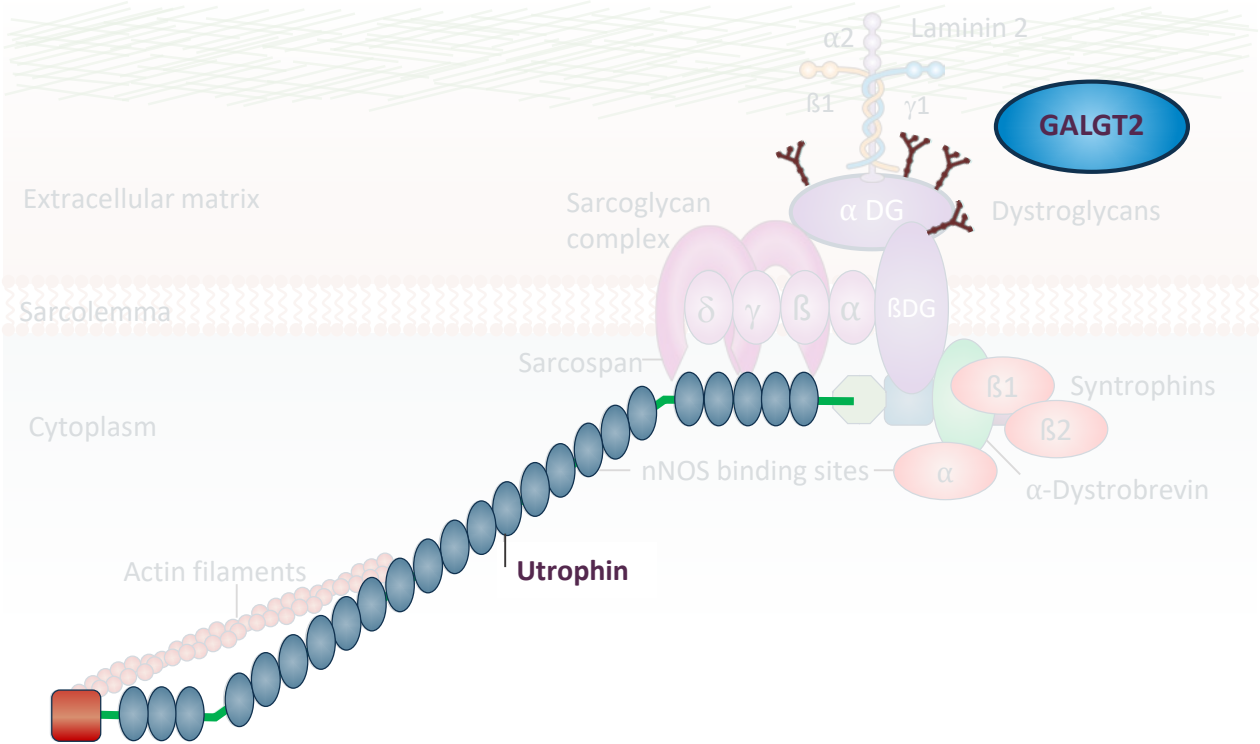
APPROACH

GALGT2 gene therapy

DISEASES

- **Duchenne muscular dystrophy**
- **Limb-Girdle Muscular Dystrophy**



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PRESENTER

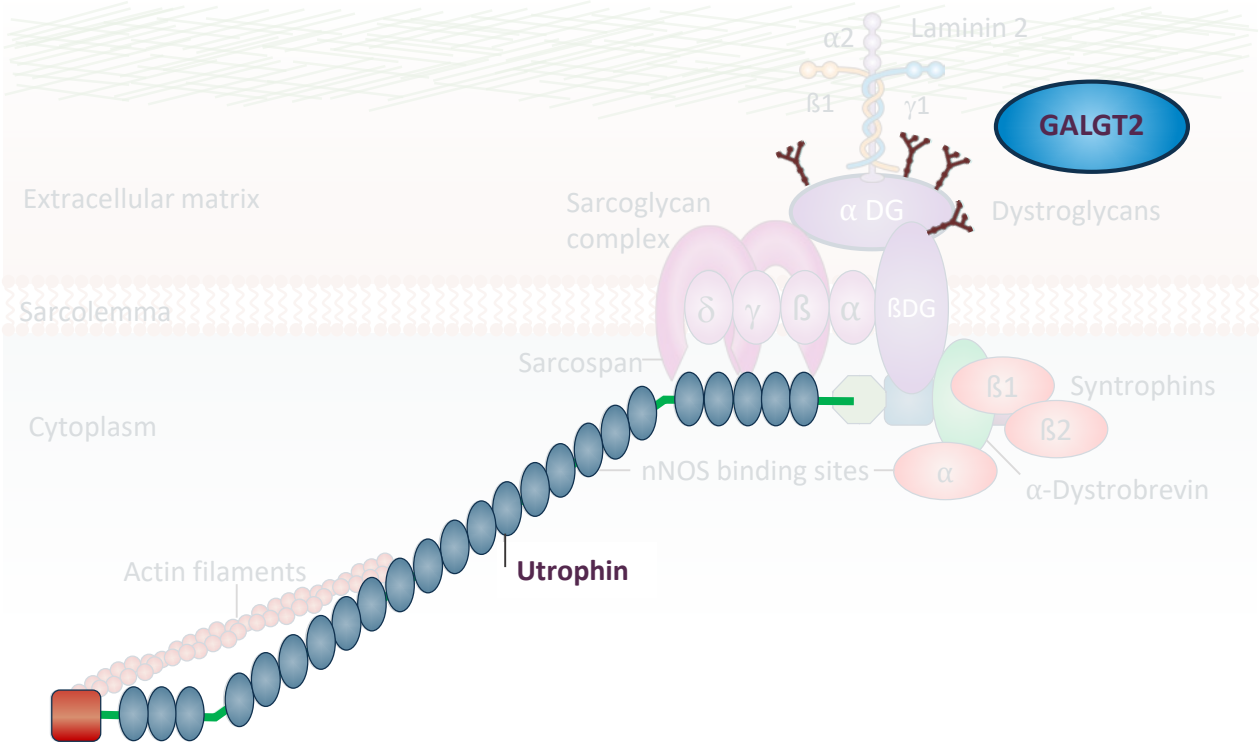
Kevin M. Flanigan, M.D.

APPROACH

GALGT2 gene therapy

DISEASES

- **Duchenne muscular dystrophy**
- **Limb-Girdle Muscular Dystrophy**
- **Merosin-Deficient Congenital Muscular Dystrophy**



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PRESENTER

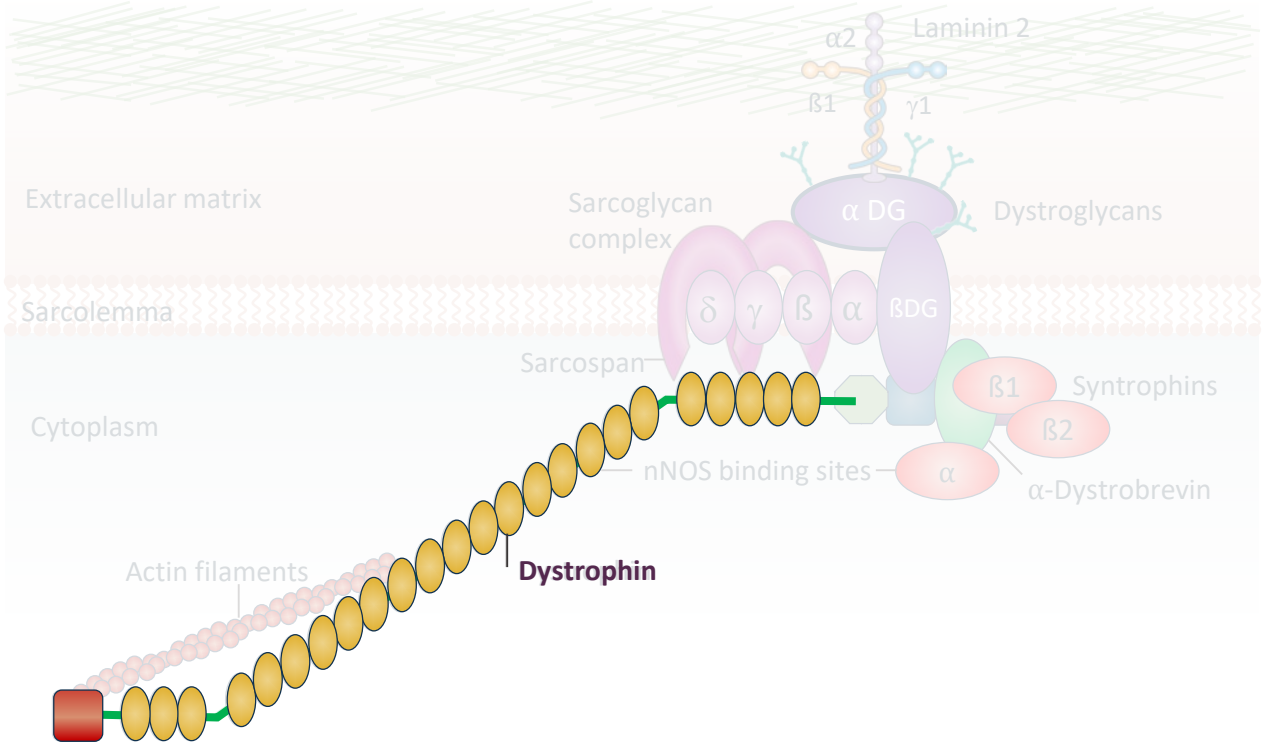
Serge Braun, Pharm.D., Ph.D.

APPROACH

Micro-dystrophin gene therapy

DISEASE

- **Duchenne muscular dystrophy**



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PRESENTERS

Jerry R. Mendell, M.D.

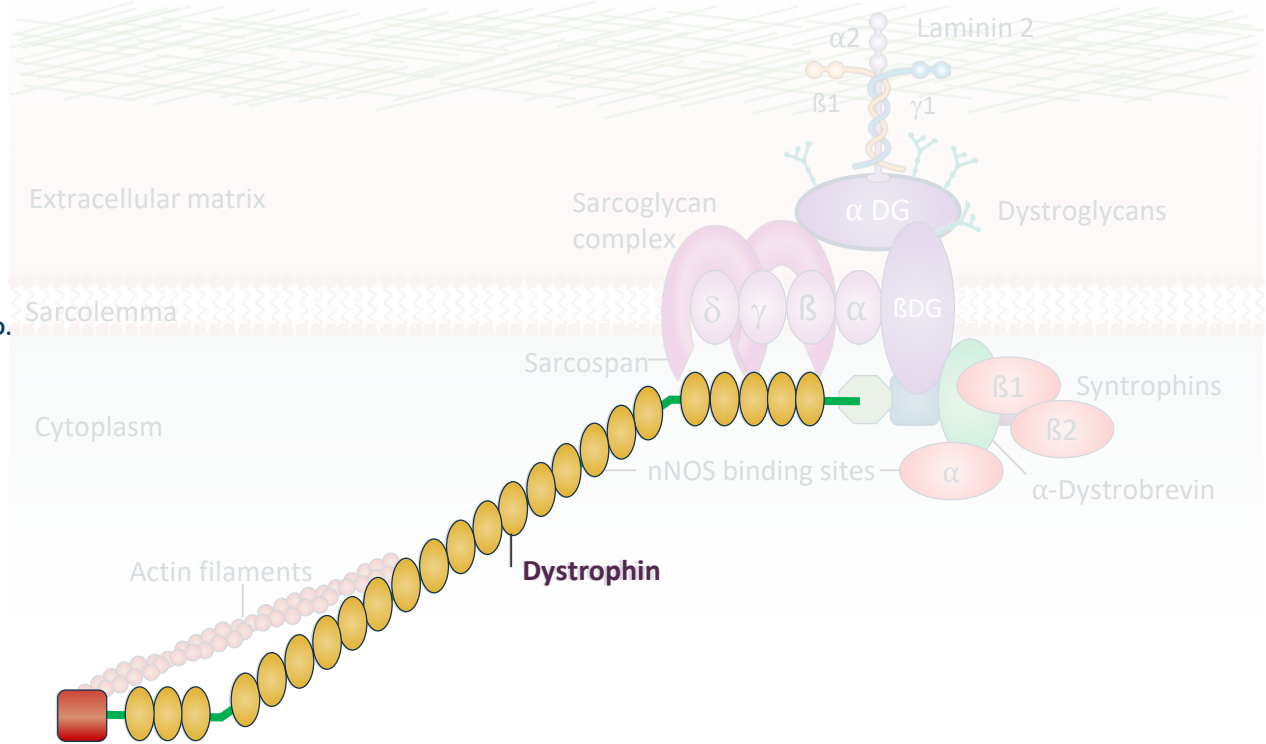
Louise Rodino-Klapac, Ph.D.

APPROACH

Micro-dystrophin gene therapy

DISEASE

- **Duchenne muscular dystrophy**



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PRESENTER

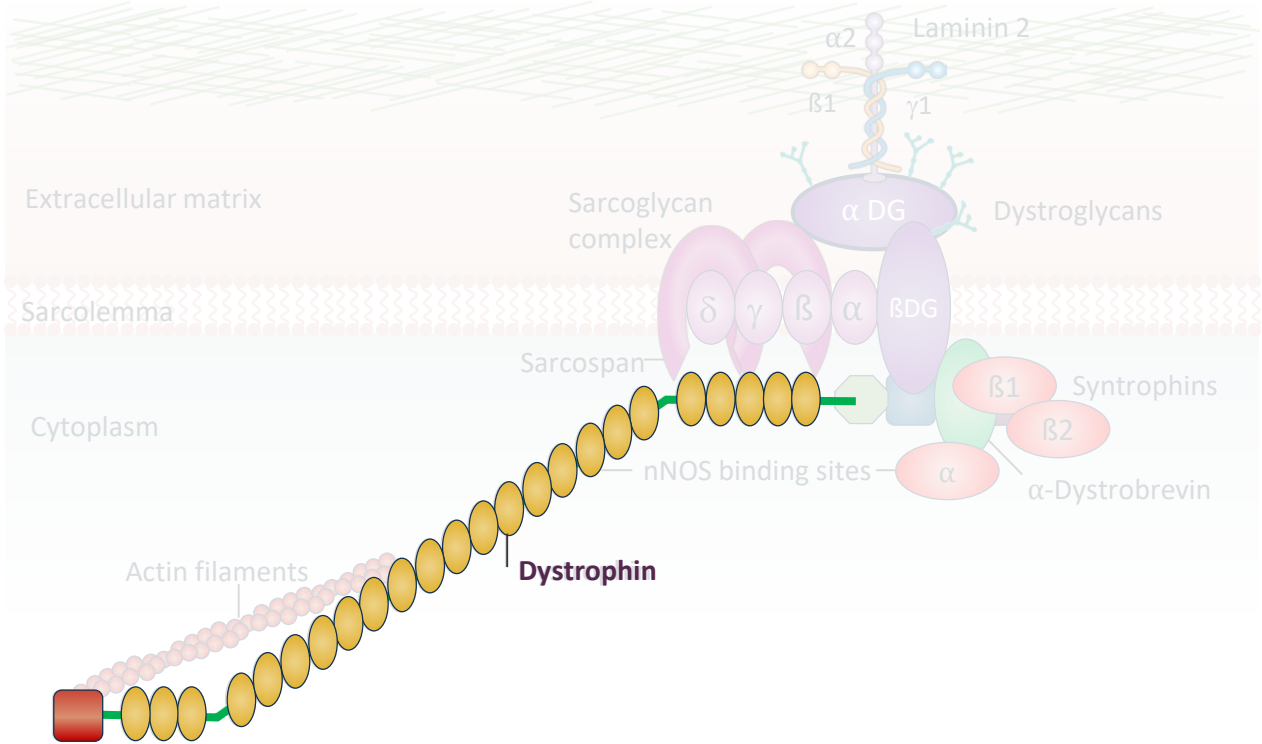
Charles A. Gersbach, Ph.D.

APPROACH

Gene editing (CRISPR/Cas9)

DISEASE

- **Duchenne muscular dystrophy**



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PRESENTER

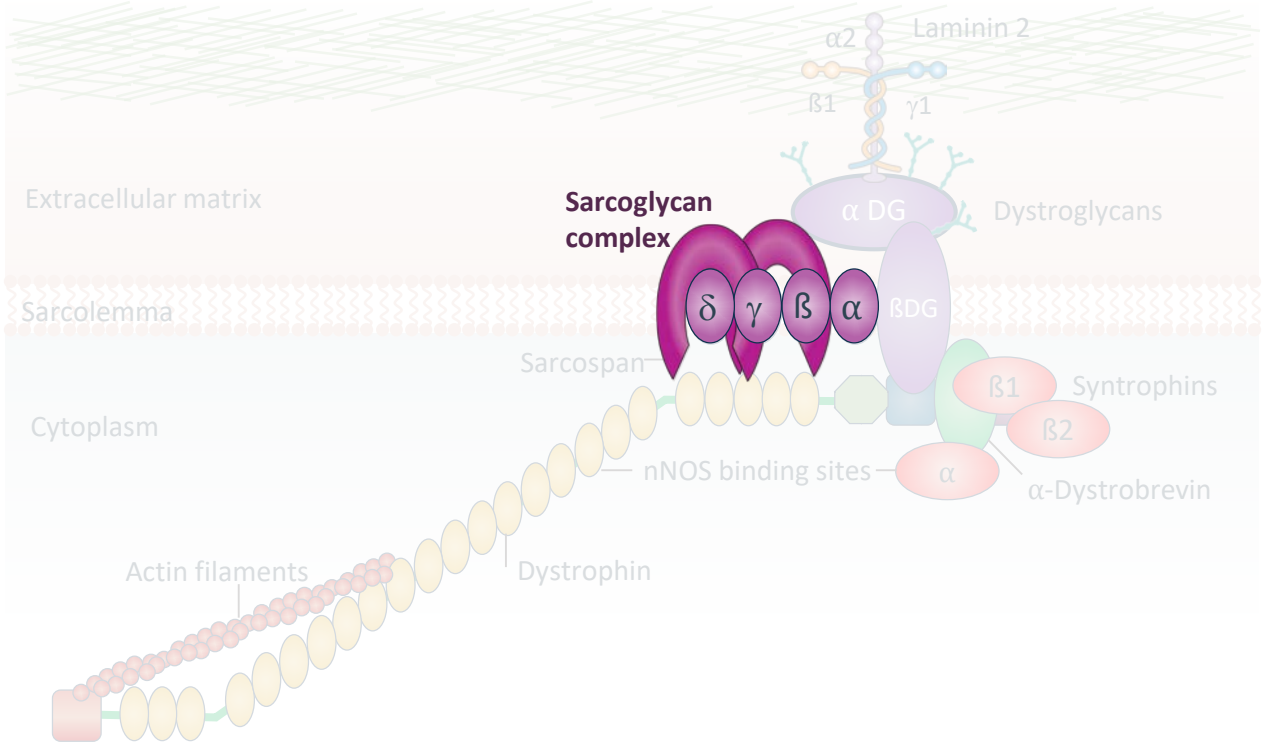
Louise Rodino-Klapac, Ph.D.

APPROACH

Gene therapy

DISEASE

- **Limb-Girdle Muscular Dystrophy**



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PRESENTER

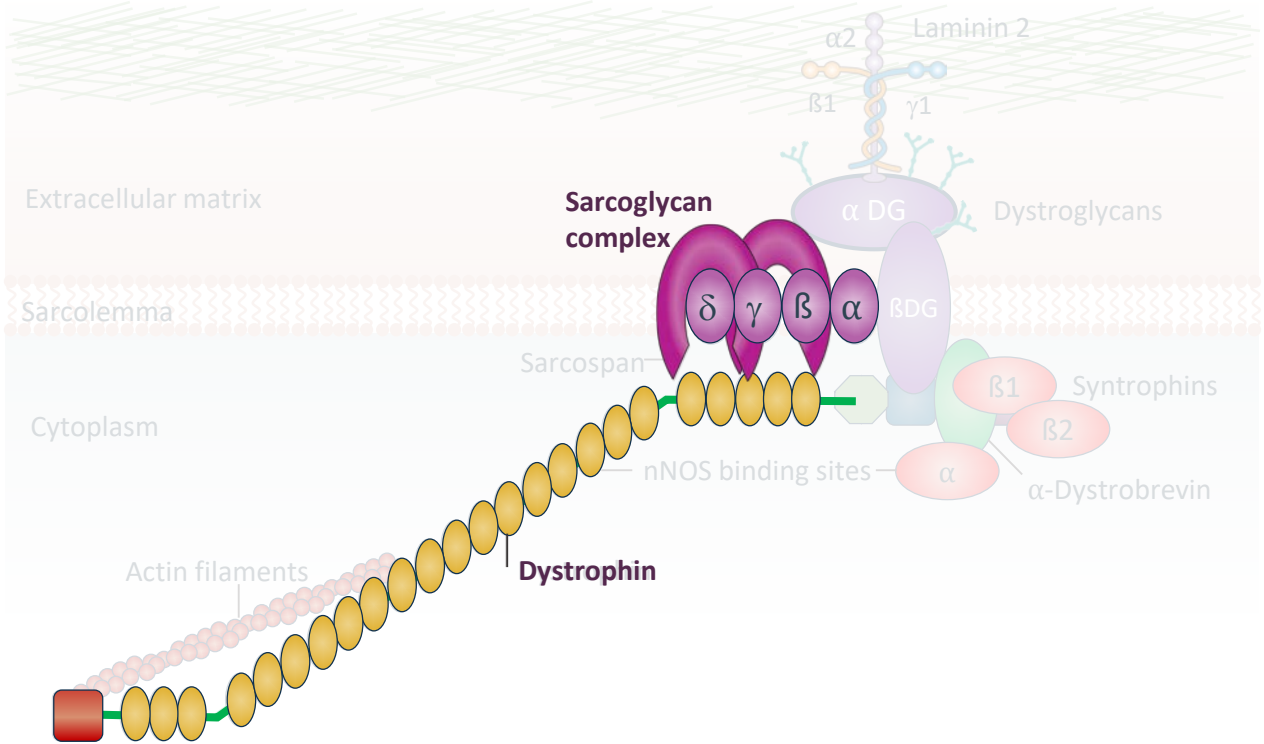
Louise Rodino-Klapac, Ph.D.

APPROACH

Gene therapy

DISEASE

- **Limb-Girdle Muscular Dystrophy**



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OUR CORE EXPERTISE IS TARGETING THE DYSTROPHIN-ASSOCIATED PROTEIN COMPLEX TO TREAT MUSCULAR DYSTROPHIES

PRESENTERS

Gunnar Hanson, Ph.D.

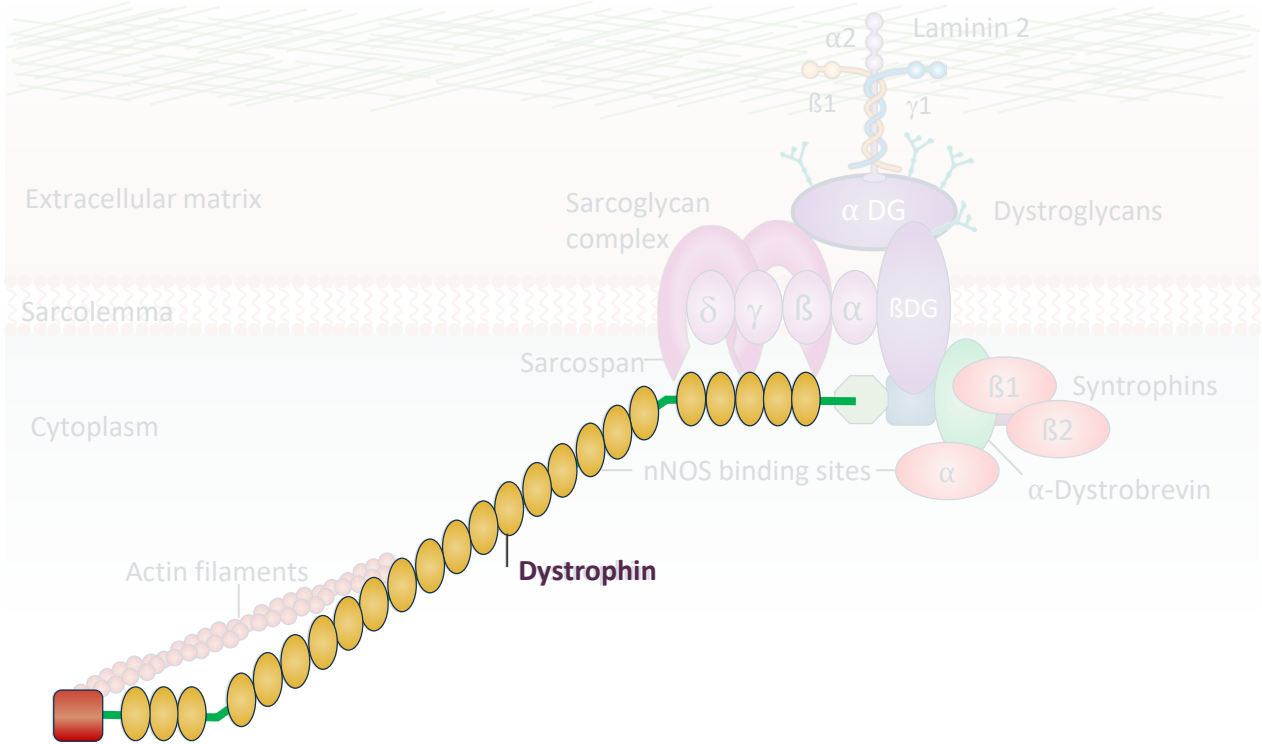
Marco Passini, Ph.D.

APPROACH

RNA-targeted therapies (exon skipping)

DISEASE

- **Duchenne muscular dystrophy**



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SAREPTA THERAPEUTICS, INC 2018 R&D DAY

A Phase 1/2 Clinical Trial of Intra-arterial Gene Transfer of rAAVrh74.MCK.GALGT2 for DMD: Initial Safety Profile

KM Flanigan, LG Chicoine, JP Cheatham, SL Cheatham, LP Lowes, M Iammarino, MA Waldrop, RA Schrader, F Rinaldi, R Xu, D Zygmunt, TR Simmons, PT Martin

Kevin Flanigan, MD

Director, Center for Gene Therapy
Nationwide Children's Hospital
Columbus, Ohio

Today's Presentation

- GALGT2 Overview
- Preclinical Data
- Clinical Data: Patient 1
- Conclusions and Next Steps

GALGT2 Overview

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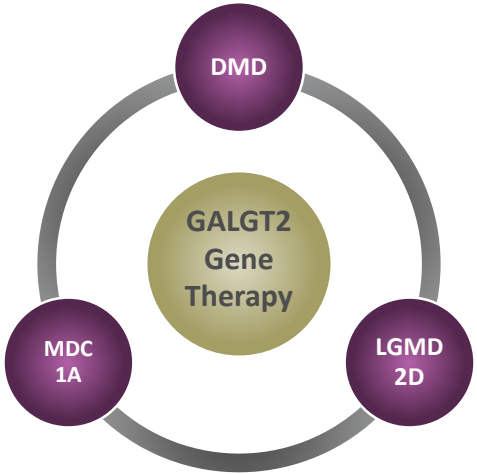
When your child needs a hospital, everything matters.℠

GALGT2 Overview – Scientific Rationale

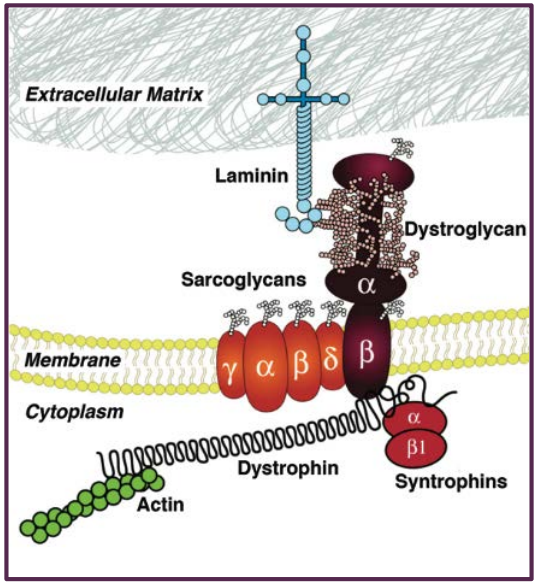
- Surrogate gene therapy that has the potential to treat *almost all patients* with dystrophin deficiencies irrespective of mutation type or location
- No expected issues with transgene immune responses since GALGT2 is endogenously expressed

Potential Treatment for Multiple Dystrophies



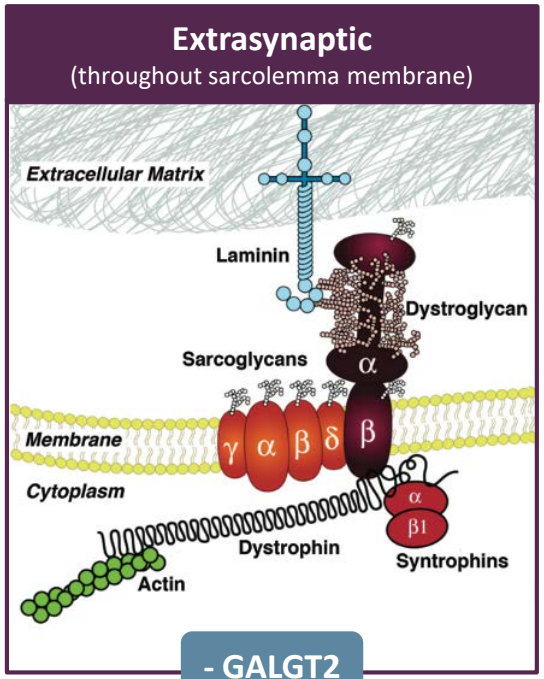
DMD, Duchenne muscular dystrophy; MDC 1A, congenital muscular dystrophy Type 1A; LGMD, Limb Girdle Muscular Dystrophy Type 2D.

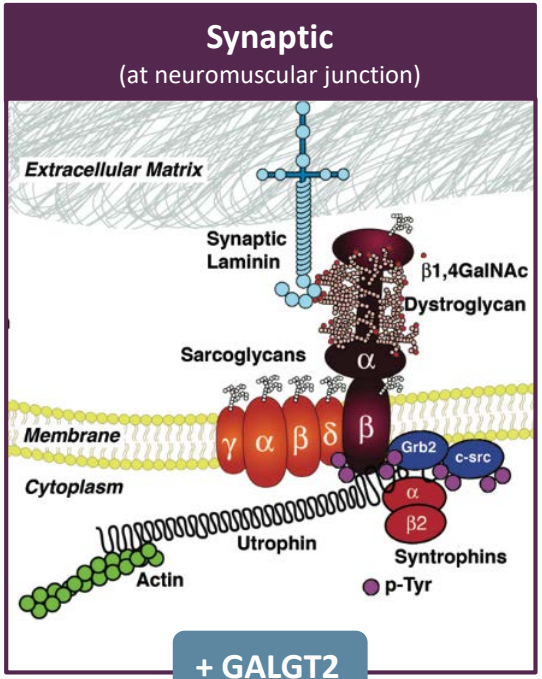
The DAG Complex Prevents Muscle Damage by Linking Intracellular Actin to the Extracellular Basal Lamina



DAG, dystrophin-associated glycoprotein.
Nguyen HH, et al. *Proc Natl Acad Sci USA*. 2002;99(8):5616-5621.

Two Dystroglycan Complexes Exist in Skeletal Muscle With Differential Expression of GALGT2





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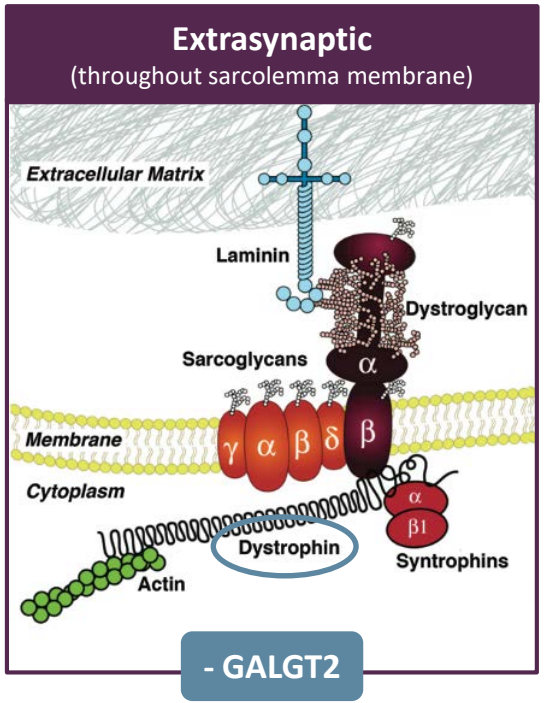

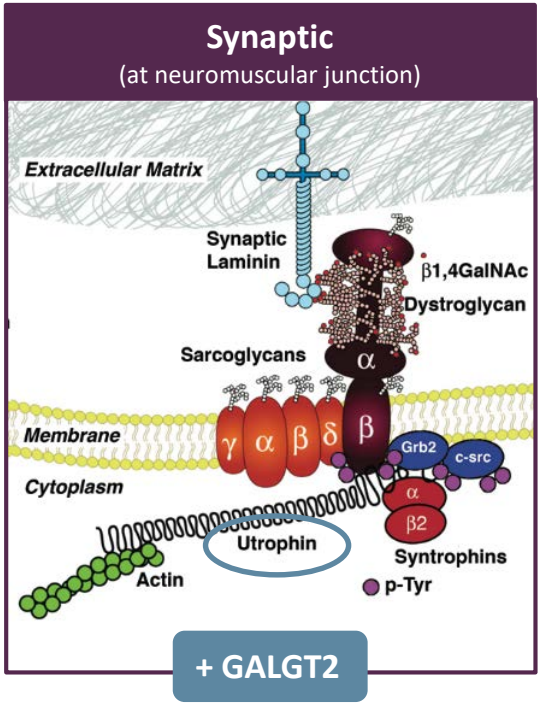

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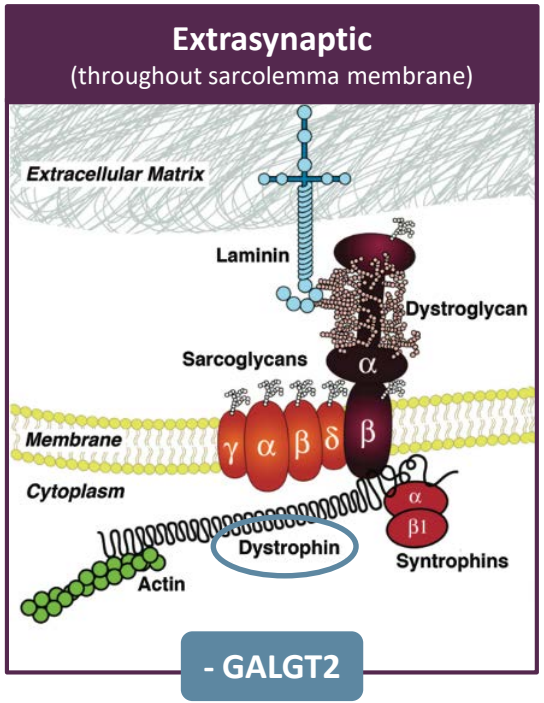
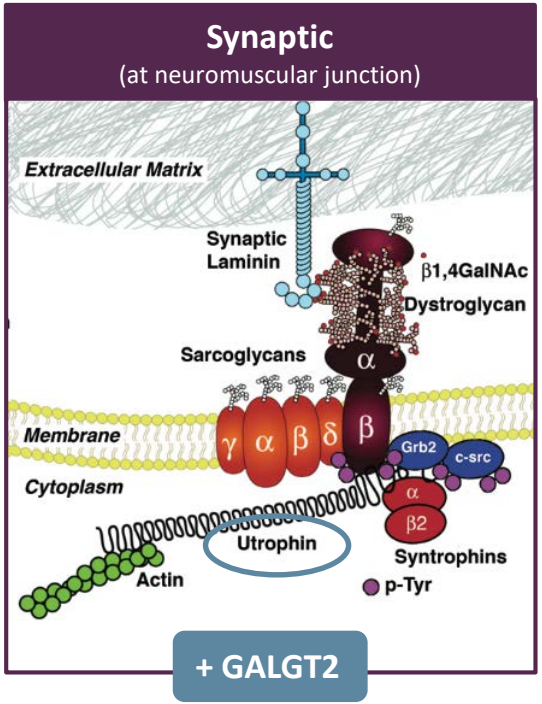


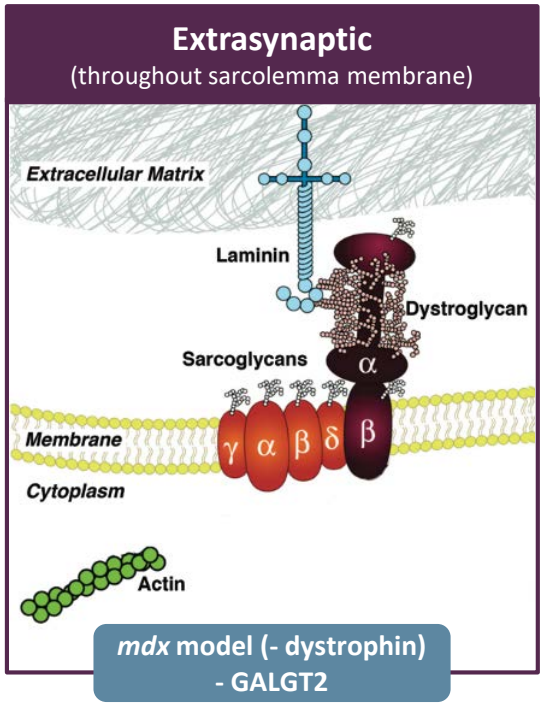


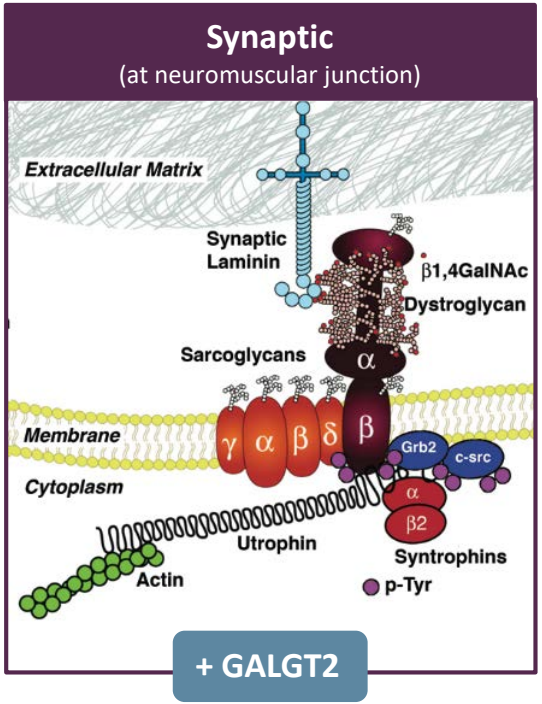
***B4GALNT2* (GALGT2)**

GALGT2 stimulates the glycosylation of α-dystroglycan

Nguyen HH, et al. *Proc Natl Acad Sci USA*. 2002;99(8):5616-5621.

In the Absence of Dystrophin, the Actin Cytoskeleton Is Still Linked to the Basal Lamina via Utrophin Expression at Neuromuscular Junctions





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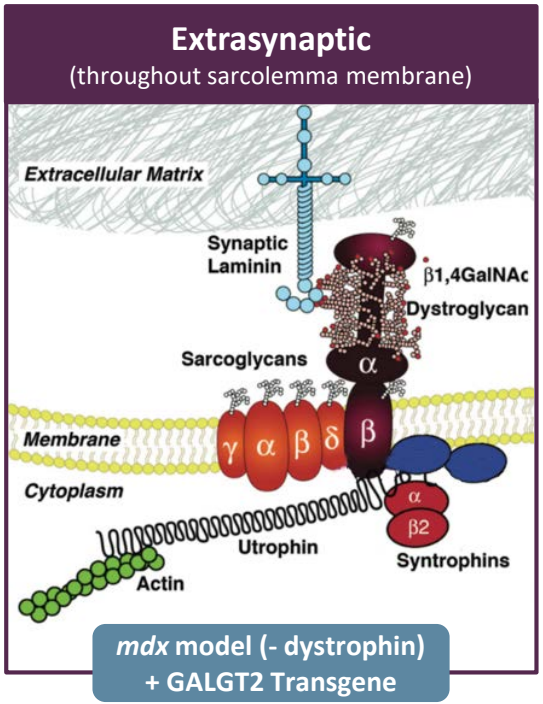
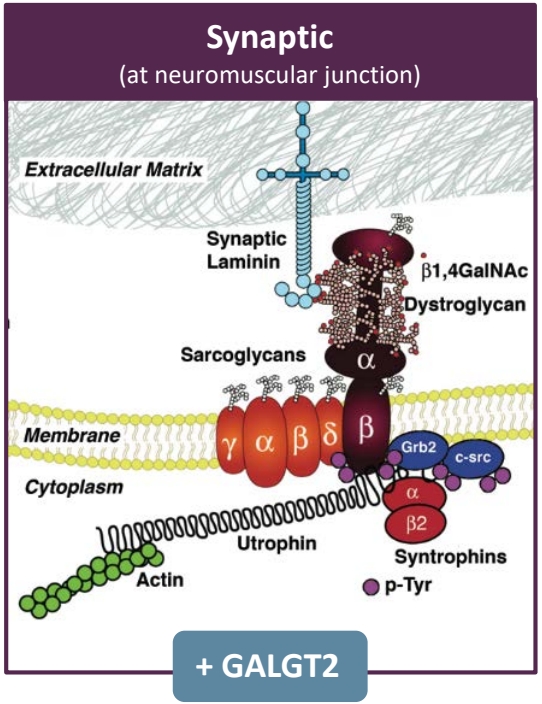
GALGT2 Transgenic Muscles Overexpress Synaptic Dystroglycan Binding Partners at Extrasynaptic Sites





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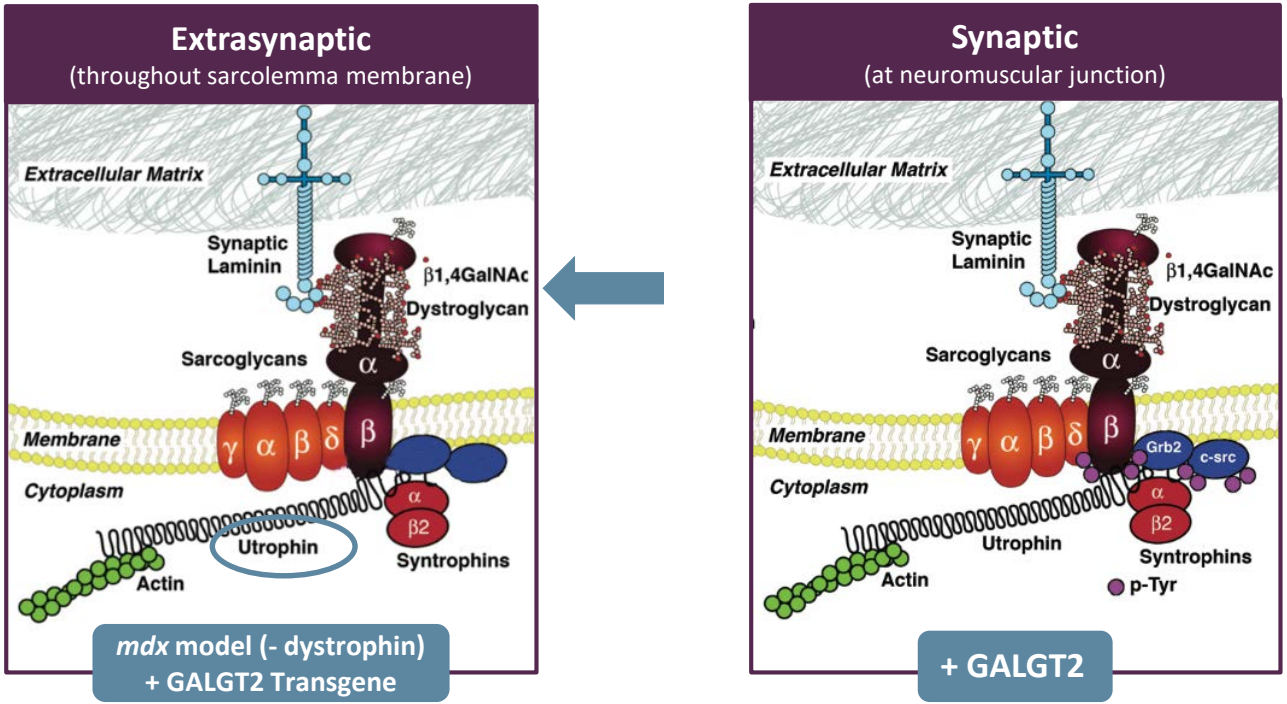

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Preclinical Data

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NATIONWIDE CHILDREN'S
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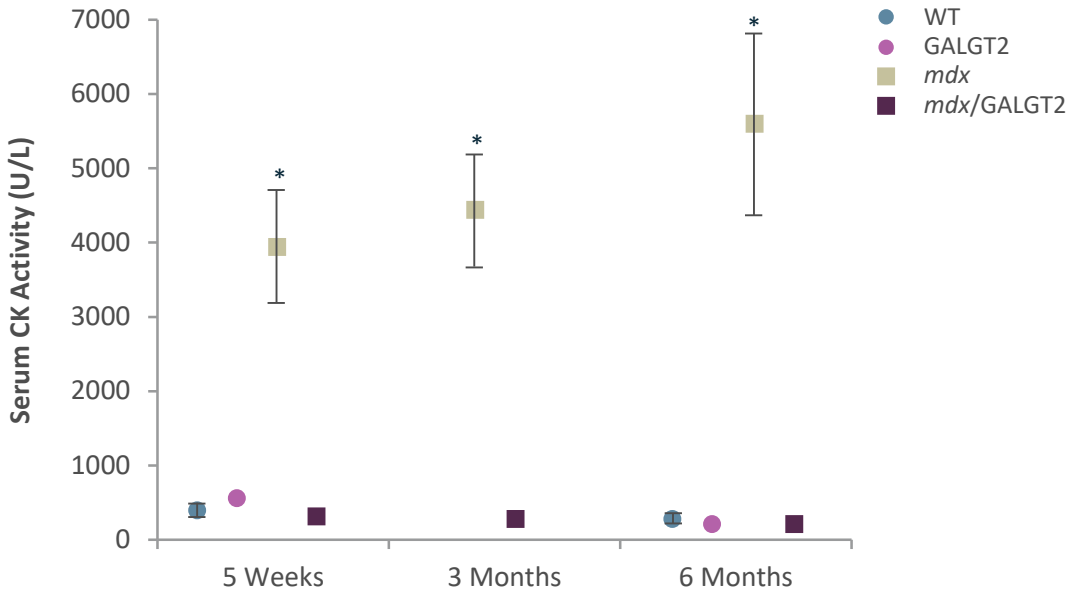
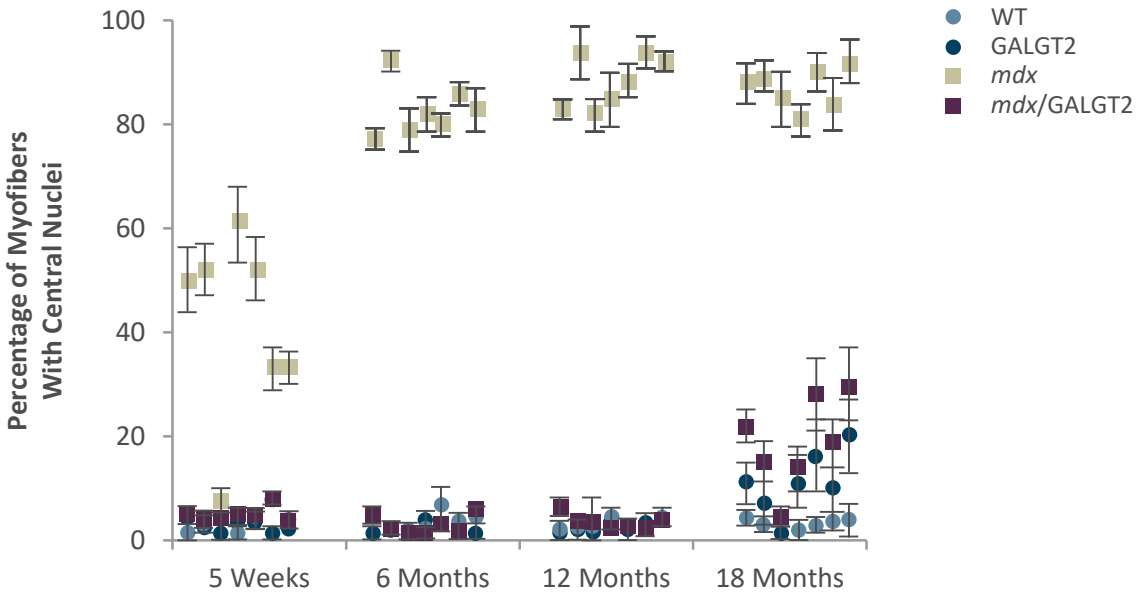
Expression of the GALGT2 Transgene in *mdx* Muscles Inhibits Elevations in Serum CK Activity



CK, creatine kinase; WT, wild type.
*Serum CK activity was reduced in *mdx*/GALGT2 (P<0.001, compared with *mdx*, for all) and was not significantly different from wild-type levels (P>0.05).
Nguyen HH, et al. *Proc Natl Acad Sci USA*. 2002;99(8):5616-5621.

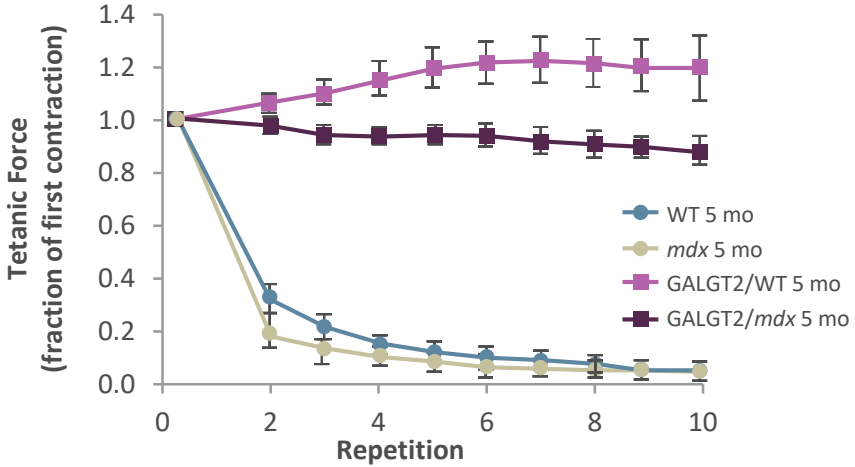
Muscle Pathology Is Absent in *mdx* Transgenic Mice Overexpressing GALGT2 for Almost the Lifespan of the Animal



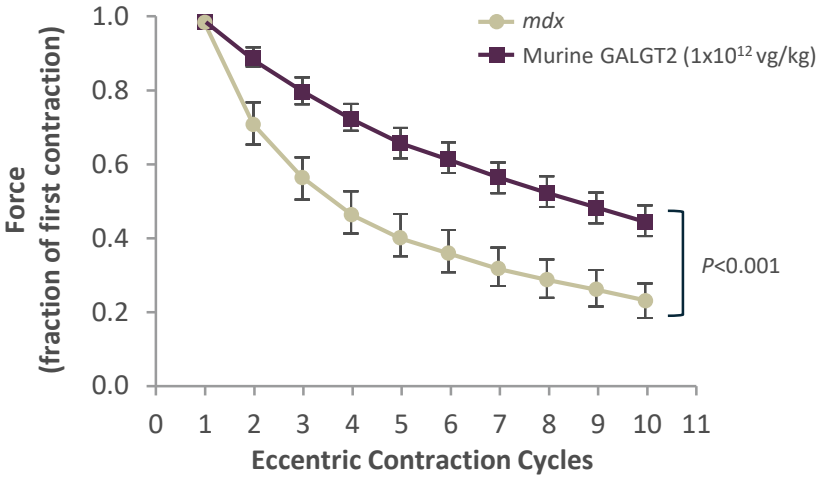
Xu R, et al. *Neuromuscul Disord*. 2007;17(3):209-220.

Overexpression of GALGT2 Results in Significant Correction of Contraction-induced Force Deficits

GALGT2 transgenic WT and *mdx* muscles are protected from loss of force during eccentric contractions



GALGT2 overexpression by AAV-mediated gene delivery protects *mdx* muscle from loss of force during eccentric contractions

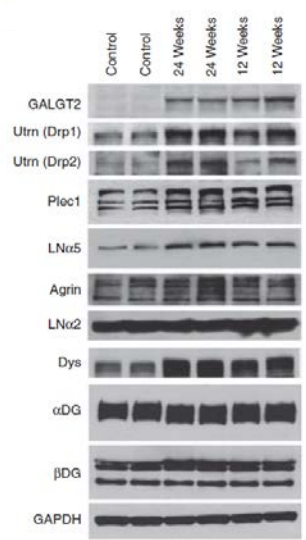


Martin PT, et al. *Am J Physiol Cell Physiol*. 2009;296(3):C476-C488.

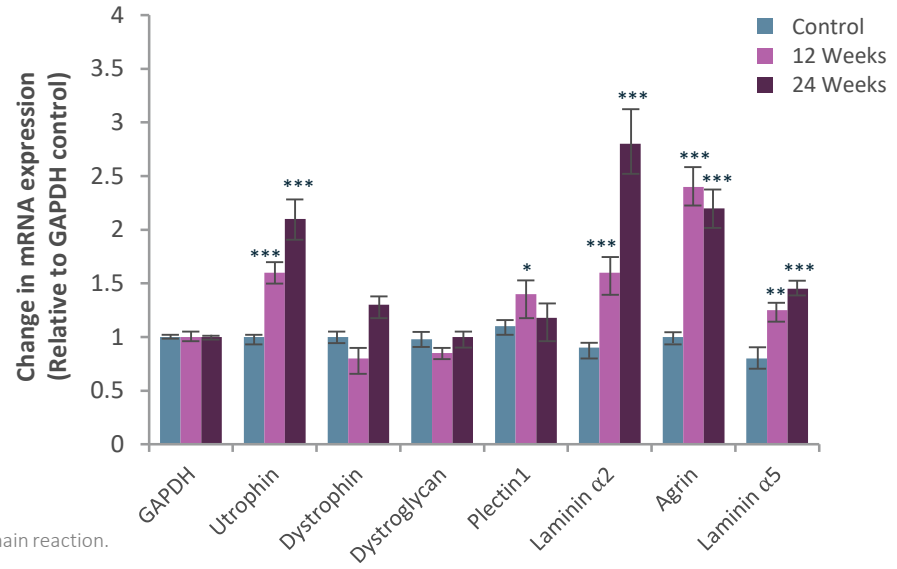
Rhesus Macaque GALGT2-treated Muscles Also Express Multiple Membrane-associated Proteins

- Serum-naïve rhesus macaques were treated with 2×10^{12} vg/kg rAAVrh74.MCK.GALGT2 via the isolated focal limb perfusion procedure for 12 or 24 weeks

Western Immunoblot



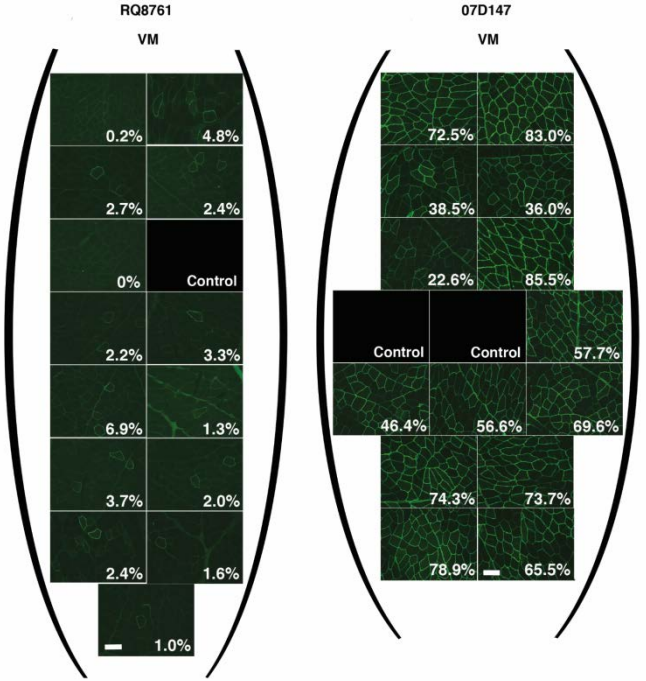
mRNA (semi-quantitative real-time PCR)



GAPDH, glyceraldehyde-3-phosphate dehydrogenase; mRNA, messenger RNA; PCR, polymerase chain reaction.
*P< 0.05; **P< 0.01;***P< 0.001.
Chicoine LG, et al. *Mol Ther*. 2014;22(4):713-724.

CT Expression Is Widespread in Gastrocnemius Muscle of Rhesus Macaques After Isolated Limb Infusion (ILI) of rAAVrh74.MCK.GALGT2

- The average % dystrophin expression is shown for each block taken from the vastus medialis (VM) muscle
- Treated using the identical ILI procedure used in clinical trial
- Dose escalation in contralateral legs in the same animal established clinical trial dose



rAAVrh74.MCK.GALGT2 Dose: $6x10^{12}$ vg/kg **$2.5x10^{13}$ vg/kg**

Xu R, et al. *Mol Ther Methods Clin Dev.* 2018. In press.

Clinical Data: Patient 1

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Phase 1/2a Gene Transfer Clinical Trial for DMD With rAAVrh74.MCK.GALGT2

IND: 16175

- **Intravascular limb infusion** for gene transfer delivered bilaterally to lower limbs via a femoral artery
- The femoral vein and artery on each side are cannulated, and catheter localization confirmed via angiography
- In one leg, blood flow is interrupted via inflation of the venous and arterial balloons, and the vector dose (of approximately 300 mL) is delivered over ~1 minute, 30 seconds
- Blood flow remains interrupted for a 10-minute dwell time
- The arterial and then the venous balloons are then deflated, and blood flow re-established
- The procedure was then repeated on the left leg

Clinicaltrials.gov. NCT03333590. Accessed June 5, 2018.

Open-label, Dose Escalation, Phase 1/2 Trial

Dose escalation planned

- Low dose (N=3): 2.5 x 10^{13} vg/kg/leg (Total: 5 x 10^{13} vg/kg)
- High dose (N=3): 5 x 10^{13} vg/kg/leg (Total: 1 x 10^{14} vg/kg)
- **Primary objective**: assessment of safety
- **Primary efficacy outcome**: expression of the CT antigen by immunofluorescence analysis
- **Secondary outcomes** include: 100MWT and NSAA

100MWT, 100-meter walk-test; NSAA, North Star Ambulatory Assessment.
Clinicaltrials.gov. NCT03333590. Accessed June 5, 2018.

Patient 1 (dosed Dec 2017)

- Enrolled at 8.4 years of age
- Mutation: Duplication of *DMD* exons 22-41
- On prednisone 10 mg/day

Baseline Clinical Assessments at Screening Visit (Nov 11, 2017)

Variable	Value
6MWT Distance (m)	357
6MWT % of Predicted Value	59.9%
100M Distance Time (sec)	103.6
100M % of Predicted Value	59.6%
NSAA Total Score (out of 34)	18

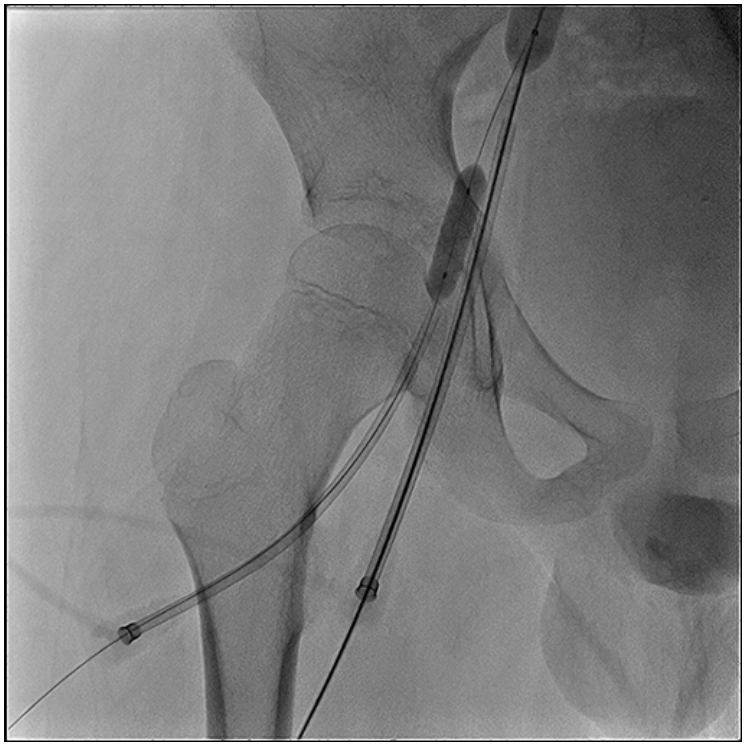
Variable	Value
FVC % of Predicted Value	85%
MVICT Max Strength (kg)	
Right knee extension	6.59
Right knee flexion	6.43
Left knee extension	6.90
Left knee flexion	5.72

6MWT, 6-minute walk test; FVC, forced vital capacity; MVICT, maximum voluntary isometric contraction testing.

Patient 1: Baseline MRI

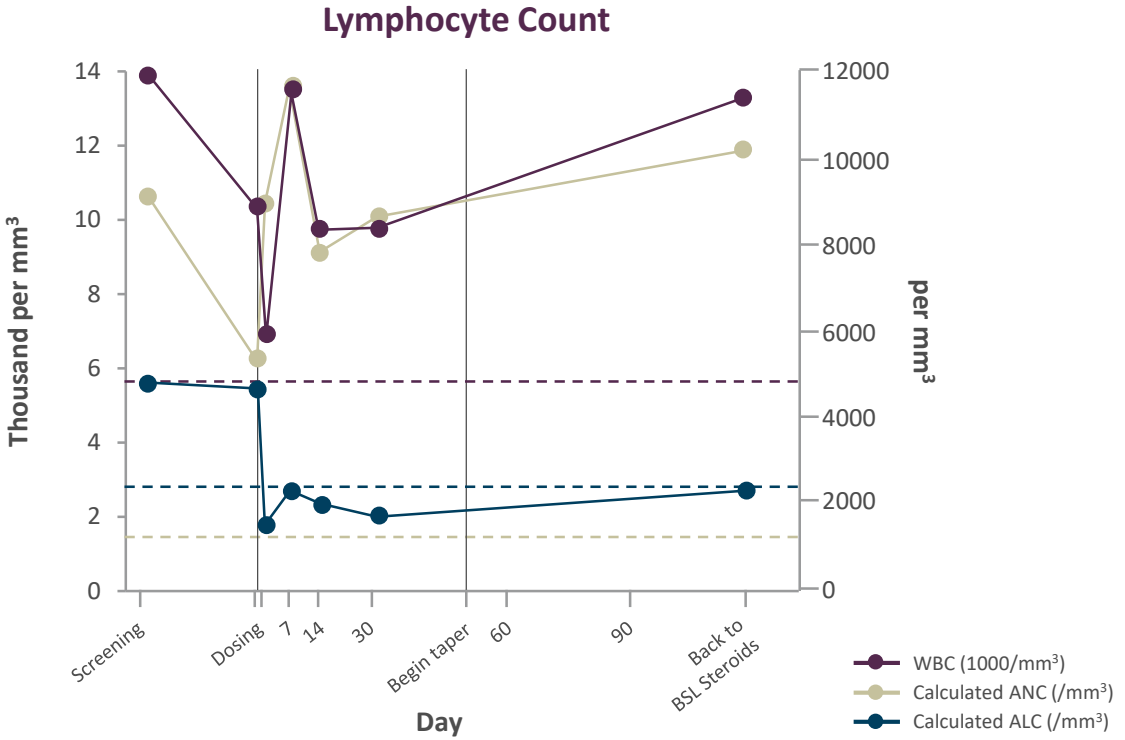
Echo, echocardiogram; MRI, magnetic resonance imaging.

Right Femoral Artery Ablation Run-off Angiogram With Balloon Occlusion



Adverse Events

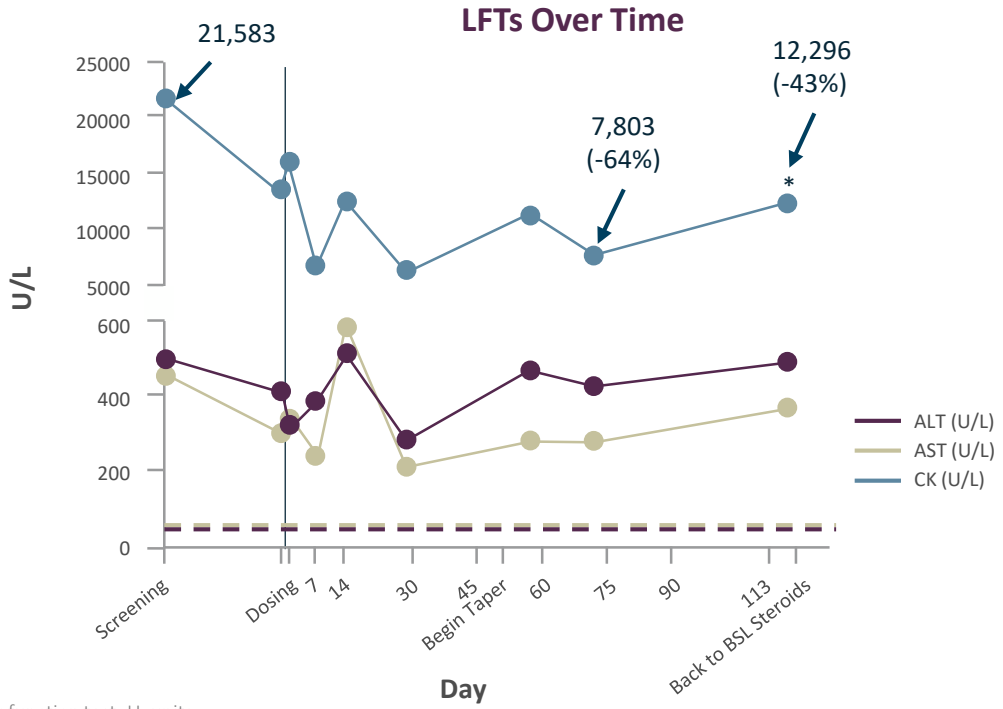
- Bruising at catheterization site (resolved by Day 30)
- Decreased ALC



ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BSL, baseline; WBC, white blood cell.

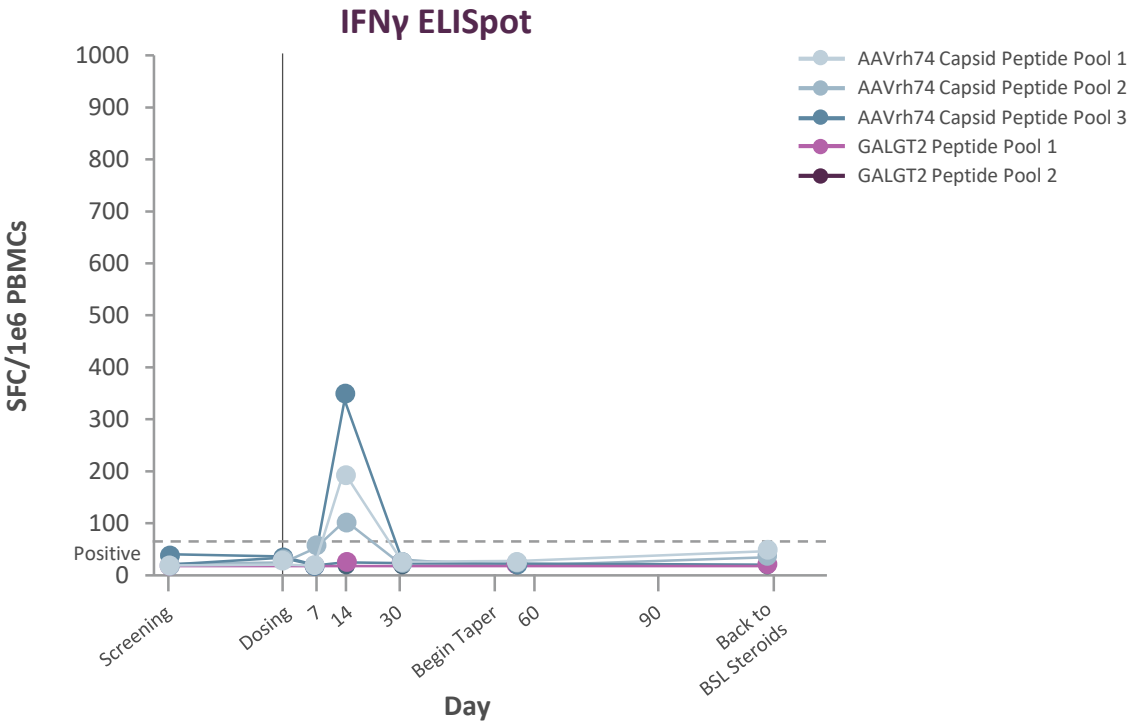
Laboratory Values: Serum Transaminases and CK

Visit	CK (37-430 U/L)
Screening	21583
Day -1	13504
Day 1	15901
Day 7	6767
Day 14	12571
Day 30	6363
Day 60	11310
Day 75	7803
Day 120	12296



ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test; U, units.
*Specimen hemolyzed.

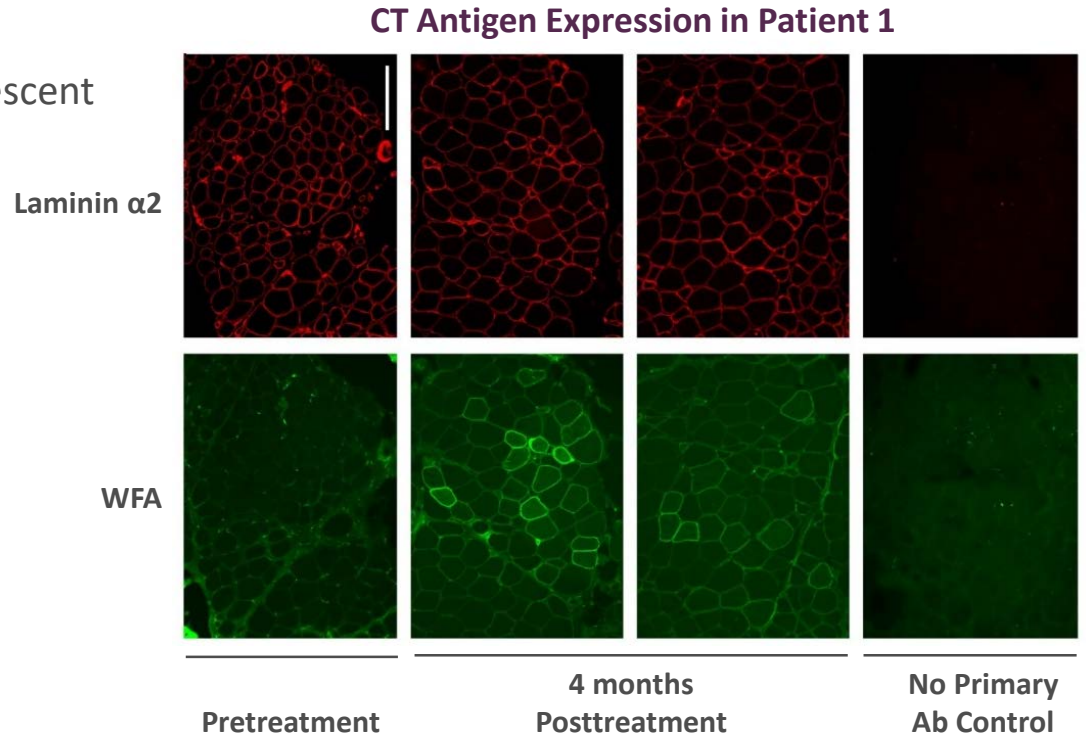
No Sustained Cellular Immune Responses to GALGT2 or to AAV Capsid



ELISpot, Enzyme-Linked ImmunoSpot; IFNγ, interferon gamma; PBMC, peripheral blood mononuclear cell; SFC, spot forming cell.

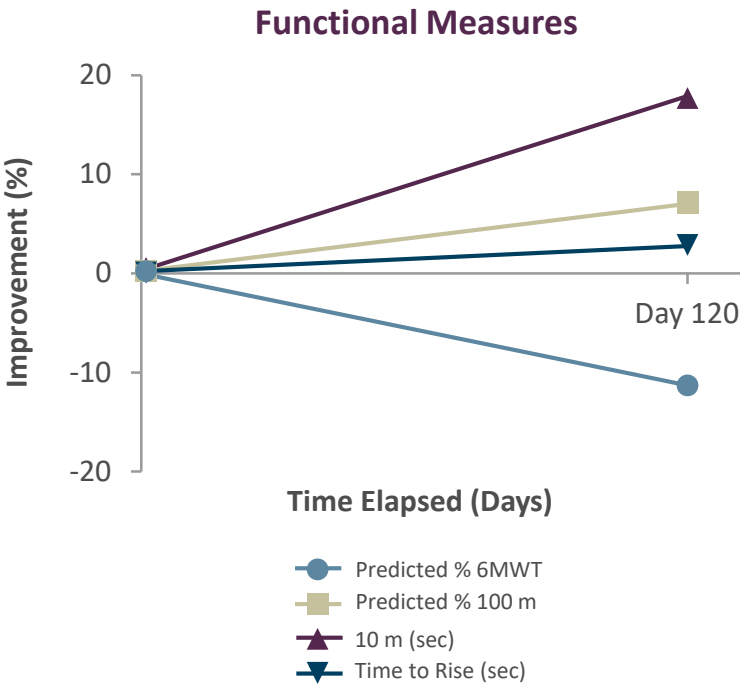
CT antigen Expression (WFA staining) Was Widely Detected in Patient 1 (Preliminary Analysis)

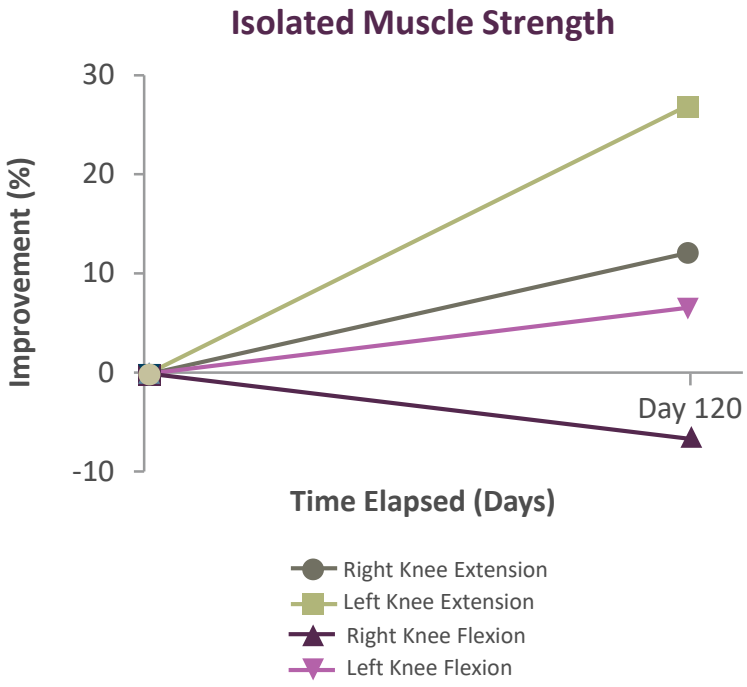
- Preliminary analysis
- Blinded, quantitative immunofluorescent assay undergoing validation



Ab, antibody; CT, cytotoxic T-cell; WFA, wisteria floribunda agglutinin.

Stability for Functional and Isolated Muscle Strength Measures Were Observed at 4 Months Postinjection





Conclusions and Next Steps

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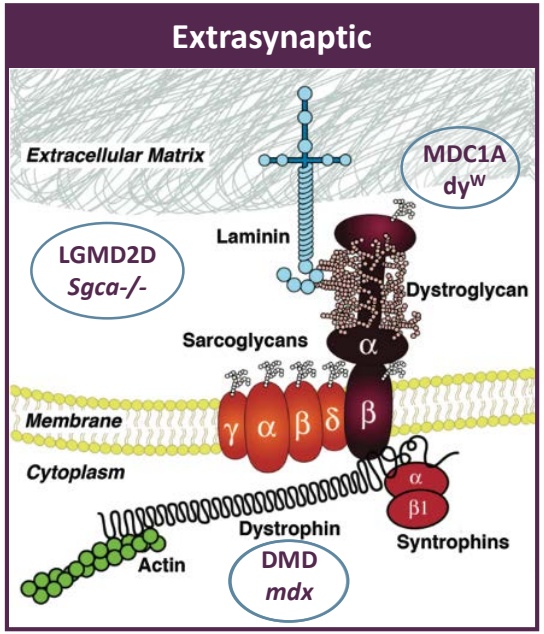
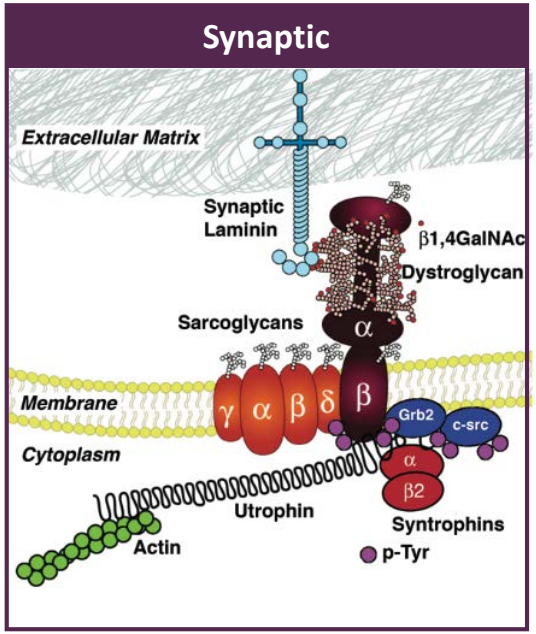
Conclusions

- rAAVrh74.MCK.GALGT2 delivery at a total of 5 x 10^{13} vg/kg via bilateral isolated limb-infusion is well tolerated
- Stability for functional and isolated muscle strength measures were observed at 4 months postinjection
- Based on results, moving toward an IND amendment
- Based on POC, next steps
  - Dose-finding studies for systemic delivery supporting an intravenous trial are underway
  - Seeking IRB approval for next subject at higher dose of 1 x 10^{14} vg/kg

IND, investigational new drug; IRB, Institutional Review Board; POC, proof of concept.

GALGT2 Shows Broad Therapeutic Potential in the Muscular Dystrophies





- GALGT2 overexpression would be therapeutic independent of the *DMD* mutation
- Because it is endogenously expressed, there are no expected issues with transgene immune responses

MDC1A, merosin-deficient congenital muscular dystrophy; Sgca, sarcoglycan.

1. Nguyen HH, et al. *Proc Natl Acad Sci* USA. 2002;99(8):5616-5621. **2.** Hoyte K, et al. *Am J Pathol*. 2004;164(2):711-718. **3.** Xu R, et al. *Neuromusc Disord*. 2007;17(3):209-220. **4.** Xu R, et al. *Am J Pathol*. 2007;171(1):181-199. **5.** Xu R, et al. *Am J Pathol*. 2009;175(1):235-247. **6.** Martin PT, et al. *Am J Physiol*. 2009;296(3):C476-C488.

Acknowledgments

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Jerry Mendell, MD
Louise Rodino-Klapac, PhD

OUR VISION FOR THE FUTURE OF

Precision Genetic Medicine

SAREPTA THERAPEUTICS, INC 2018 R&D DAY

Micro-dystrophin Gene Therapy Approach for the Treatment of Duchenne Muscular Dystrophy

Serge Braun, PharmD, PhD

Chief Scientific Officer, AFM-Téléthon

Director, Neuromuscular Strategy, Genethon

President, Genosafe SAS

Member, French National Academy of Pharmacy

SAREPTA THERAPEUTICS

OUR VISION FOR THE FUTURE OF

Precision Genetic Medicine

SAREPTA THERAPEUTICS, INC 2018 R&D DAY

Today's Presentation

- AFM-Téléthon overview
- DMD and micro-dystrophin gene therapy overview
- Preclinical studies of micro-dystrophin gene therapy in the *mdx* and *Dmd*^{mdx} models
- Preclinical studies of micro-dystrophin gene therapy in the GRMD model
- Summary and next steps

DMD, Duchenne muscular dystrophy; GRMD, golden retriever muscular dystrophy.

AFM-Téléthon

- Since 1987, a national, festive, and supportive event
  - 30-hour live television marathon
  - 200,000 volunteers
  - 20,000 local events
  - 5 million participants
  - 1 million donors on World Duchenne Awareness Day
- Budget: ~$140 M

AFM-Téléthon website. www.afm-telethon.com. Accessed June 8, 2018.

AFM-Téléthon:
$75 M/Year in R&D; $1.6 B Since 1987

- 300 R&D programs/year
- 400 peer-reviewed publications/year
- 55 proprietary patent families
- 35 active clinical trials in 30 different diseases (~50% neuromuscular)

AFMTÉLÉTHON
CURE THROUGH INNOVATION

→ An international network of academic research groups

CEA, French Alternative Energies and Atomic Energy Commission (Commissariat à l'énergie atomique et aux énergies alternatives); IND, investigational new drug;
INSERM, French National Institute of Health and Medical Research (Institut national de la santé et de la recherche médicale); NMD, neuromuscular disease; R&D, research and development.

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GENETHON
CURE THROUGH INNOVATION

Gene Therapy for Rare Diseases

- 8 products at clinical or IND stage
- 180 staff
- *Not for profit*

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I-Stem CURE THROUGH INNOVATION

Stem Cell R&D

- 2 IND applications
- Automated screening on disease cell models
- 80 staff
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Stem Cell R&D

- 2 IND applications
- Automated screening on disease cell models
- 80 staff
- *Not for profit*

Reference Center for NMDs

- 270 staff (Hospital/INSERM/ Paris University/CEA)
- *Not for profit*

Industrial Platform for Cell & Gene Therapy

- 157 staff
- *For profit*

CEA, French Alternative Energies and Atomic Energy Commission (Commissariat à l'énergie atomique et aux énergies alternatives); IND, investigational new drug;
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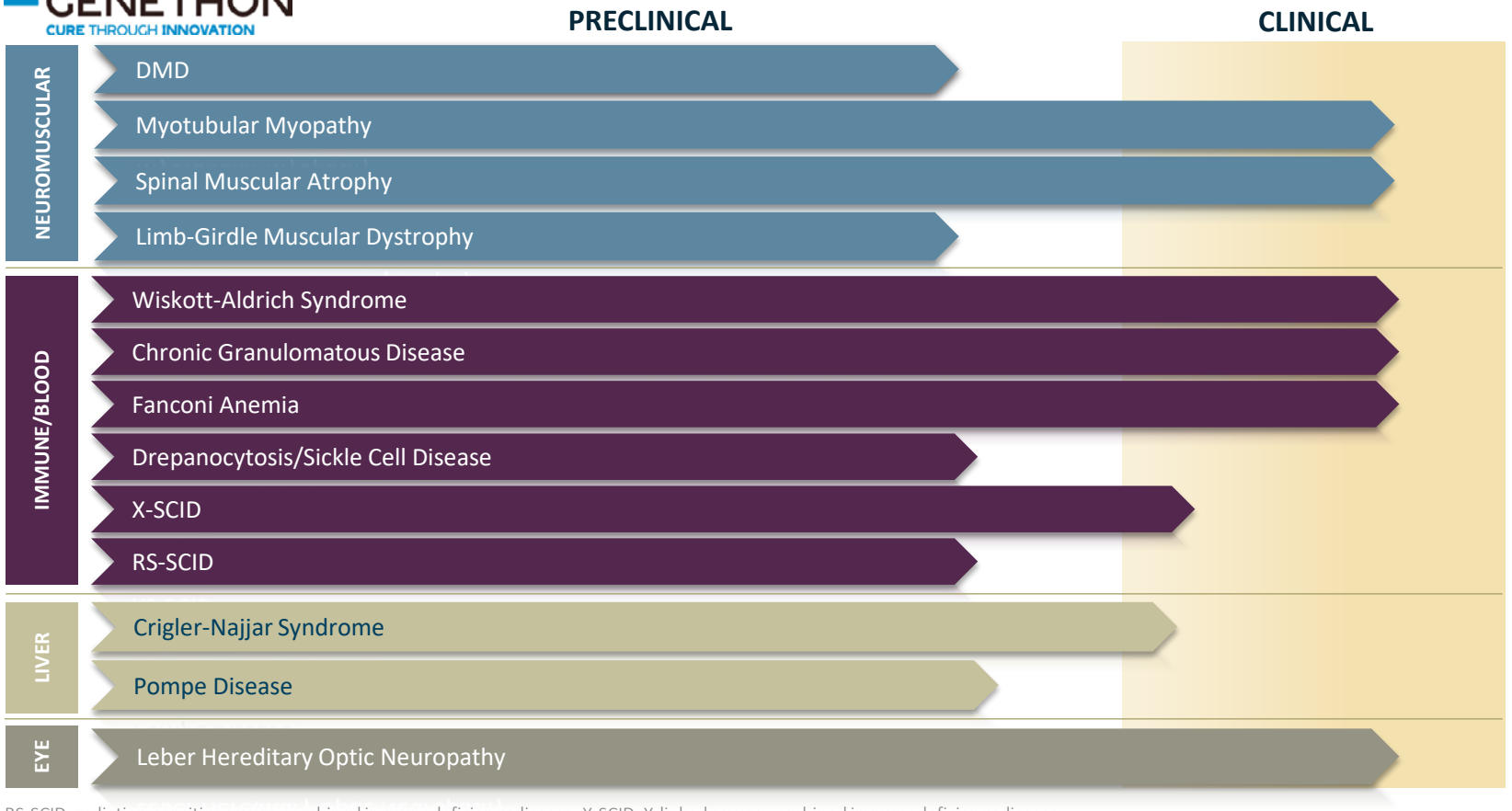
GENETHON
CURE THROUGH INNOVATION



RS-SCID, radiation-sensitive severe combined immunodeficiency disease; X-SCID, X-linked severe combined immunodeficiency disease.

Yposkesi: Gene Therapy Manufacturing Capacities

YPOSKESI

• 50,000 ft^2 GMP manufacturing plant — Process development, manufacturing, and quality control	• 45,000 ft^2 GMP manufacturing plant
• 8000 ft^2 R&D labs — R&D for cell therapy and gene therapy, analytical development	—
• Commissioned in 2013	• Commissioning expected in 2021
Gene Therapy Clinical Batches	**Gene Therapy Commercial Batches**
• Lentivirus and AAV production adherence and suspension processes	• 2 independent manufacturing suites — Up to 400 L bioreactor scale
• 4 multiproduct and independent manufacturing facilities	• Operational capacity up to 40 batches/year
• 2 independent fill-and-finish suites	• BSL2, class C
• Dedicated R&D capacity for ex vivo gene therapy (CD34$^+$ cell transduction)	—

AAV, adeno-associated virus; BSL2, Biosafety Level 2; CD34, cluster of differentiation 34; GMP, good manufacturing practice; L, liter.

Images courtesy of Serge Braun.

AAV-Micro-dystrophin Gene Therapy for DMD

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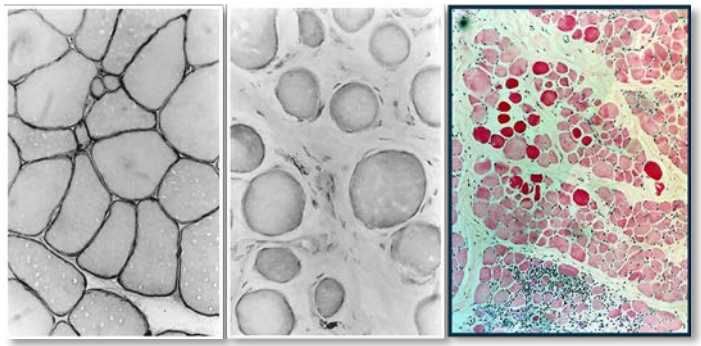
GENETHON
CURE THROUGH INNOVATION

DMD

- X-linked recessive inheritance
- Dystrophin deficiency
- Muscle fiber loss, fibrosis, and inflammation
  - Progressive muscle wasting, fatal
- ~20,000 patients in the United States and Europe
  - ~200,000 patients globally
- Corticosteroids, respiratory support
- Exon-skipping therapy is only available for a subset of patients

Healthy Muscle | **DMD**



Images courtesy of Serge Braun.

>2-5 years

Images courtesy of George Dickson.

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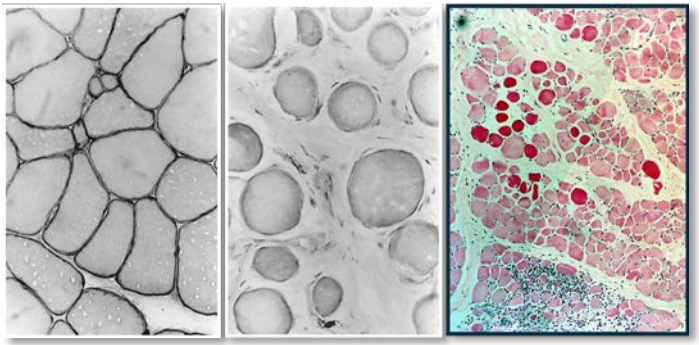

Images courtesy of Serge Braun.

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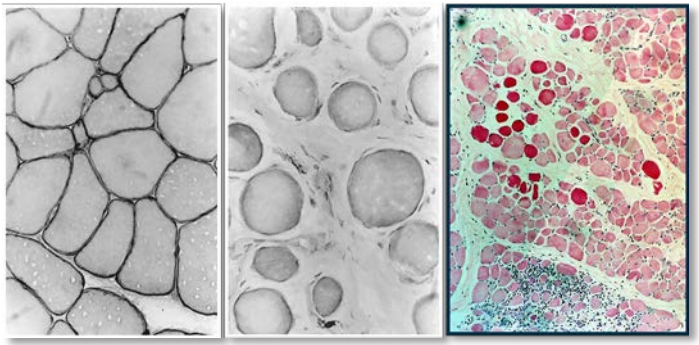

Images courtesy of Serge Braun.

>2-5 years | **>5-10 years** | **>10-12 years**

Images courtesy of George Dickson.

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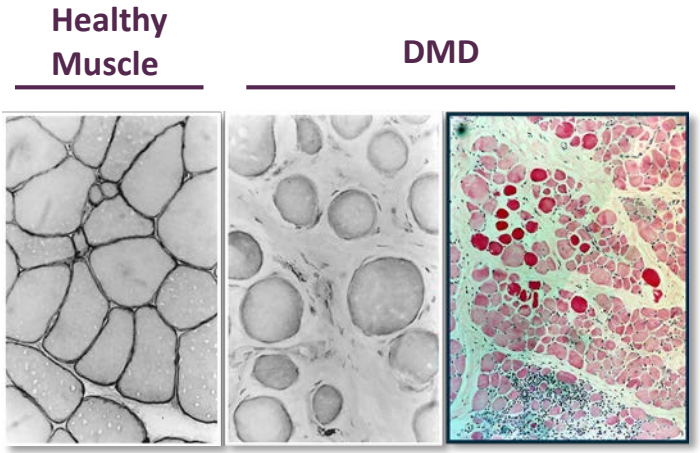


Images courtesy of Serge Braun.

Images courtesy of George Dickson.

Treatment Approach: Replace/Compensate the Defective Gene

Gene Transfer

- Micro-dystrophin
- Follistatin
- Mini-utrophin
- Dystrophin gene transfer using *trans*-splicing rAAV vectors
- Exon skipping: rAAV-U7 snRNA or U1 snRNA
- Genome editing coming down the pipeline

AAV Vector

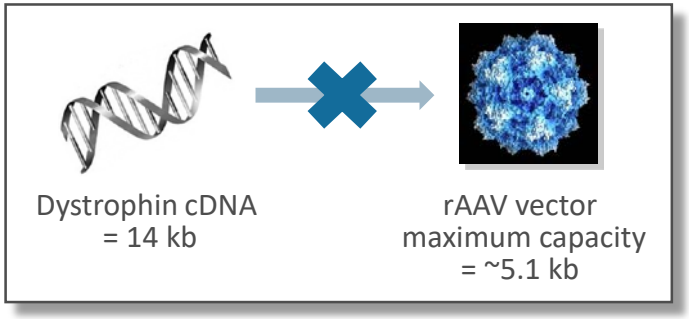


Image courtesy of Serge Braun.

Points to Consider

- Full-length dystrophin is too big for most viral vectors
- Therapeutic index of shorter versions of the dystrophin gene
- Large-scale AAV vector production remains a challenge
- Repetitive dosing: currently infeasible due to neutralizing antibodies

cDNA, complementary deoxyribonucleic acid; kb, kilobase; rAAV, recombinant AAV; snRNA, small nuclear ribonucleic acid.

Treatment Approach: Replace/Compensate the Defective Gene

Full-length Dystrophin

Full-length 3686 aa, 14 kb

Images courtesy of Serge Braun.

Design of the Therapeutic Gene

- Codons optimized for tRNA frequency, GC content, and mRNA stability
- Consensus Kozak sequence to improve initiation of translation
- mRNA optimizations leading to >30-fold increase in expression
- Muscle- and heart-specific (SPC5-12) promoter
- Expression with muscle-tropic AAV2/8 vector
- Mouse, canine, and human sequence variants

Micro-dystrophin Constructs

Micro-dystrophin-1 (3.6 kb)

Electron Microscope Image of AAV2/8-Micro-dystrophin-1

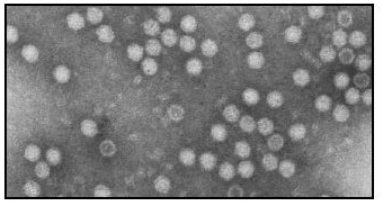


Image courtesy of Genethon.

aa, amino acid; GC, guanine-cytosine; mRNA, messenger RNA; nNOS, neuronal nitric oxide synthase; PAR-1b, partitioning-defective 1b; SP, synthetic promoter; tRNA, transfer RNA.

1. Foster H, et al. *Mol Ther*. 2008;16(11):1825-1832.
2. Li X, et al. *Nat Biotechnol*. 1999;17(3):241-245.

Preclinical Studies of AAV2/8-Micro-dystrophin-1 in *mdx* and *Dmd*^{mdx} models

SAREPTA THERAPEUTICS

GENETHON
CURE THROUGH INNOVATION

AAV2/8-Micro-dystrophin-1: Robust Dystrophin Expression in *mdx* Model

- Micro-dystrophin is expressed in the TA of *mdx* subjects treated with AAV2/8-micro-dystrophin

Western Blot Analysis of TA Tissue

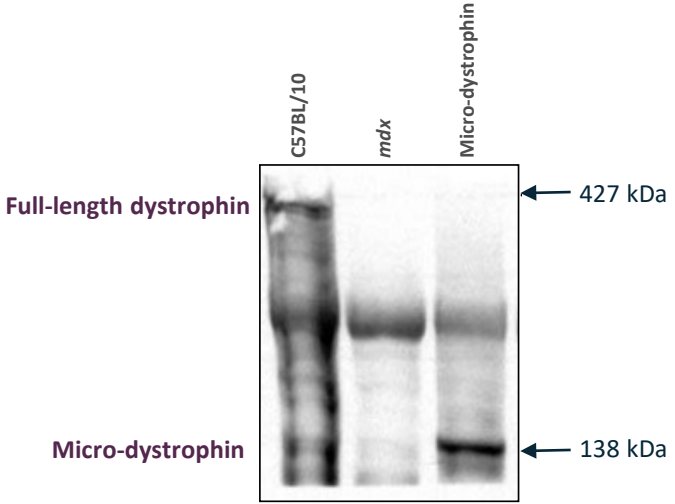
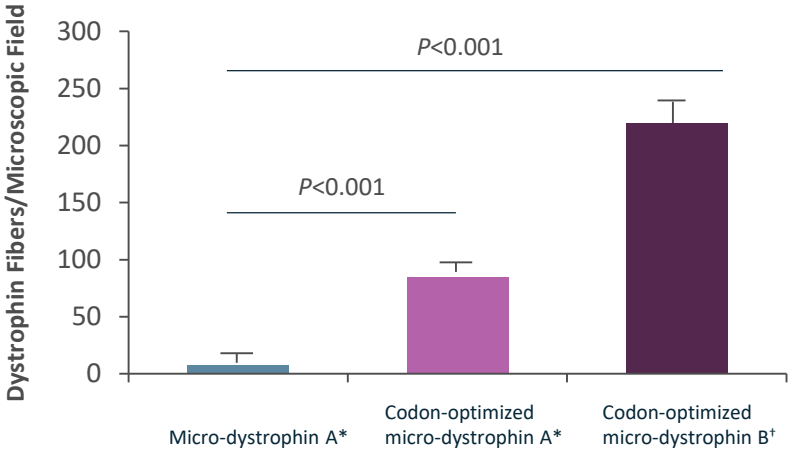


Image courtesy of Serge Braun.

- Treatment with AAV2/8-micro-dystrophin significantly increases the number of dystrophin-positive fibers in the myocardium of 10-week-old *mdx* subjects

Dystrophin-positive Fibers in Myocardium

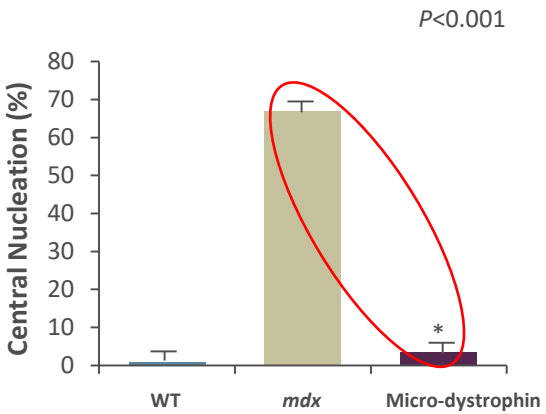


*ΔAB/R3-R18/ΔCT.
†ΔAB/R4-R23/ΔCT.
CT, C-terminal; kDa, kilodalton; TA, tibialis anterior.
Foster H, et al. *Mol Ther*. 2008;16(11):1825-1832.

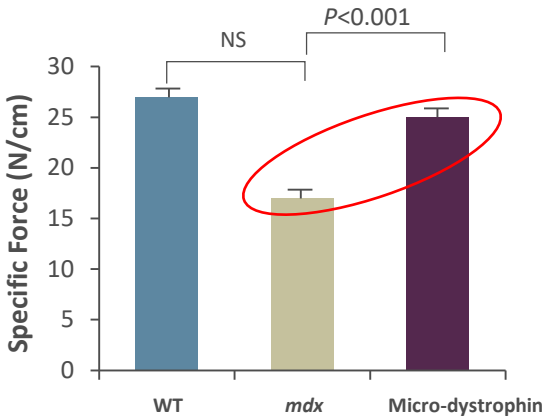
AAV2/8-Micro-dystrophin-1: “Curative” in the *mdx* Model

- Intramuscular delivery of micro-dystrophin improves morphological properties of *mdx* muscle

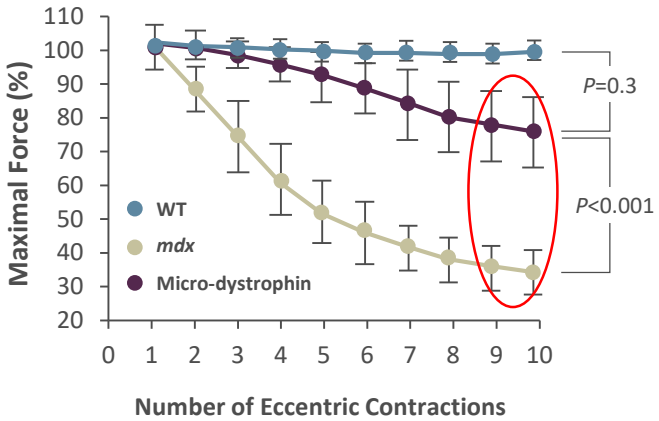
Normalized Tissue Turnover



Normalized Muscle Force



Normalized Resistance to Eccentric Contraction



*P<0.001 vs *mdx* and no significant difference vs WT.
NS, not significant; WT, wild type.
Foster H, et al. *Mol Ther*. 2008;16(11):1825-1832.

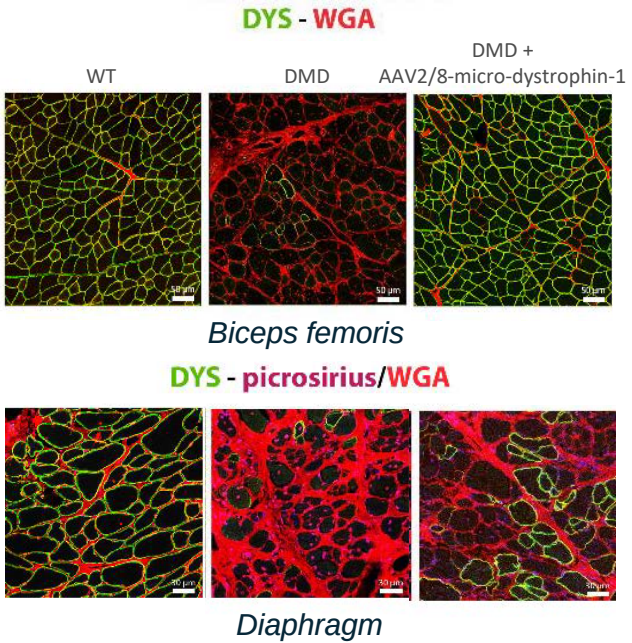
Comparison of Pathological and Functional Characteristics Between Patients With DMD and DMD Preclinical Models

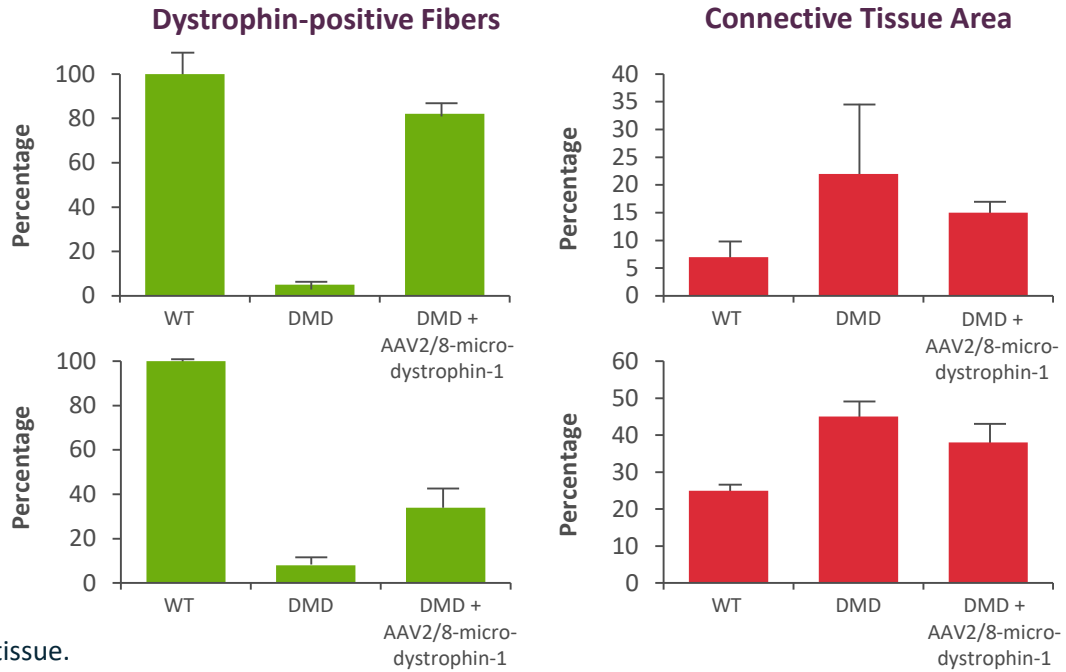
	Patient With DMD	GRMD Model	*mdx* Model	*Dmd*^{mdx} Model
Muscle histopathology				
Revertant fibers	1%-3%	<1%	5%	5%
Necrotic fibers	0.5%-3.5%	2%	<20%	>10%
Regeneration	ND	15%	10%	10%
Calcification	Mild	Mild to marked	Mild	Absent
Fibrosis	Marked	Present	Late in diaphragm (16 months)	Marked
Adiposis	Marked	Absent	Absent	Present
Cardiomyopathy	***Marked, major cause of death***	Mild	Absent or very mild	***Marked***
Muscle function				
Strength reduction	Marked	Marked	Mild	Marked
Locomotion	Severely Impaired	Impaired	Normal	Impaired

ND, not determined.

Larcher T, et al. *PLoS One*. 2014;9(10):e110371.

High Levels of Dystrophin Expression in the Biceps Femoris and Diaphragm of *Dmd*^{mdx} Subjects Treated With AAV2/8-Micro-dystrophin-1 Are Associated With Reduced Connective Tissue

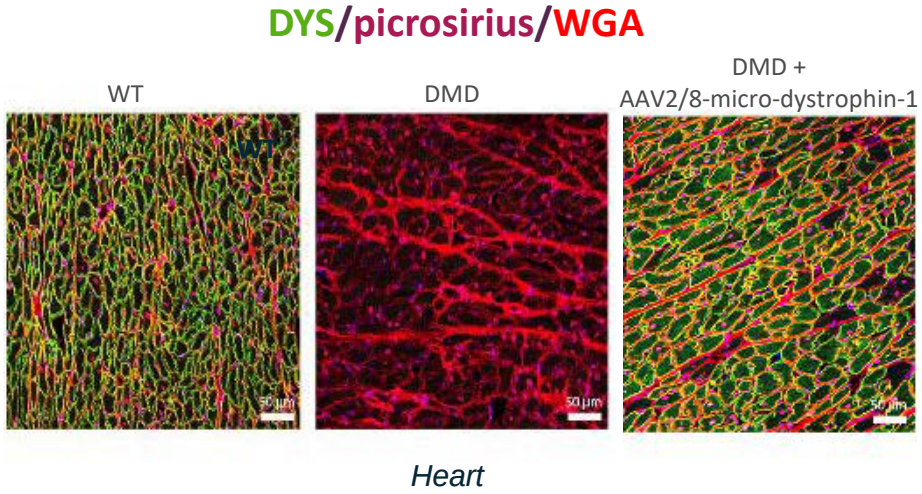


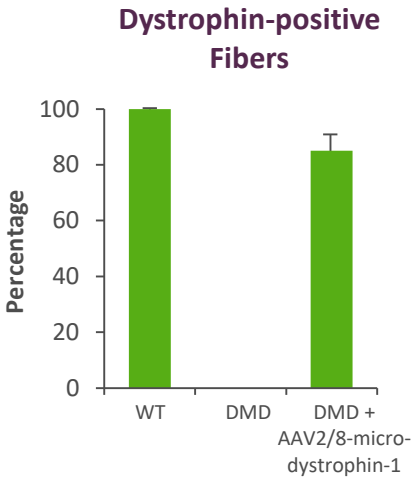


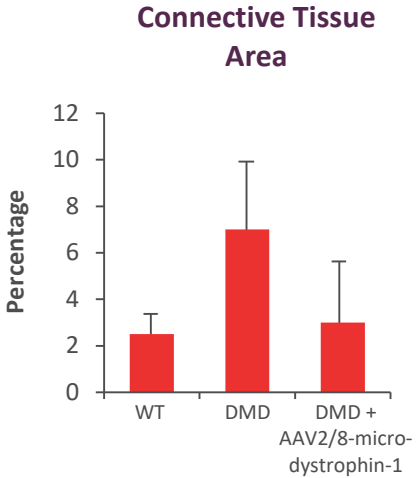
DYS: dystrophin; **picrosirius:** fibrosis; **WGA:** connective tissue.

hMD1, human micro-dystrophin-1; WGA, wheat germ agglutinin.
Unpublished data from the laboratory of Serge Braun.

High Levels of Dystrophin Expression in the Heart Muscle of *Dmd*^{mdx} Subjects Treated With AAV2/8-Micro-dystrophin-1 Are Associated With Reduced Connective Tissue



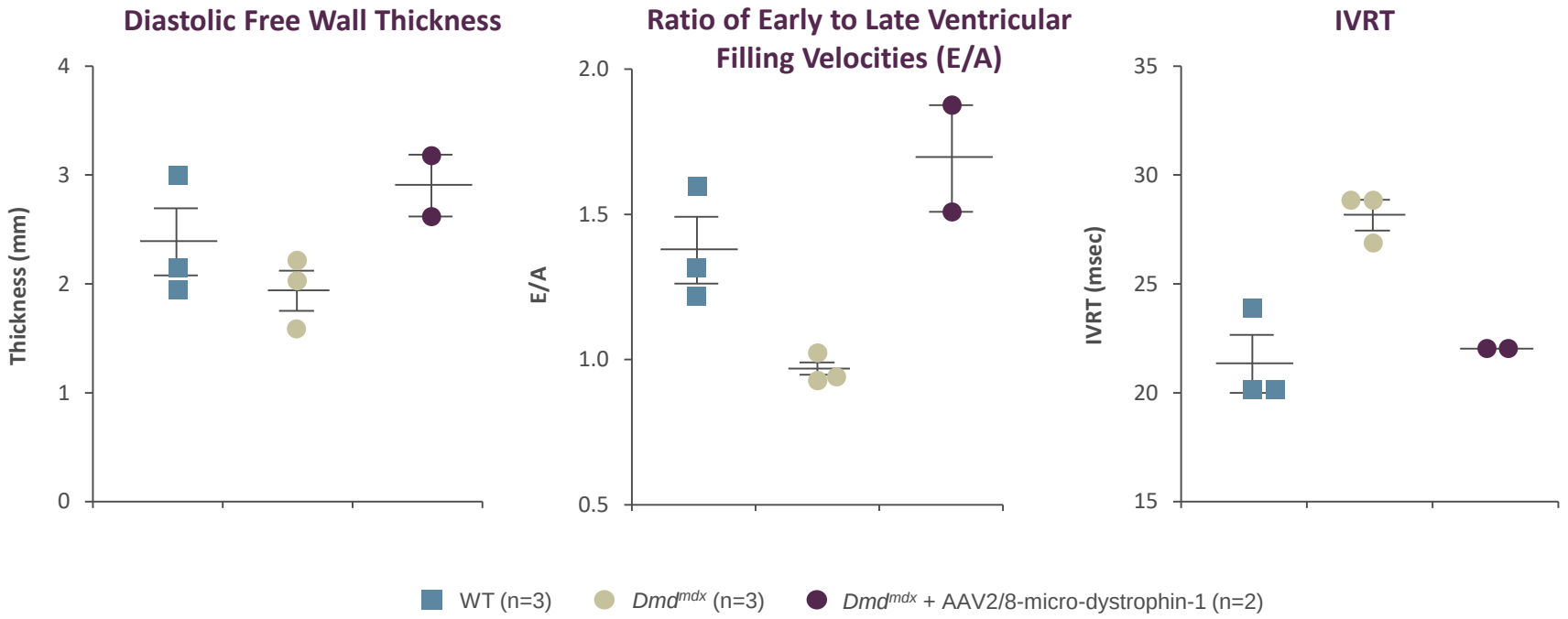




DYS: dystrophin; **picrosirius:** fibrosis; **WGA:** connective tissue.

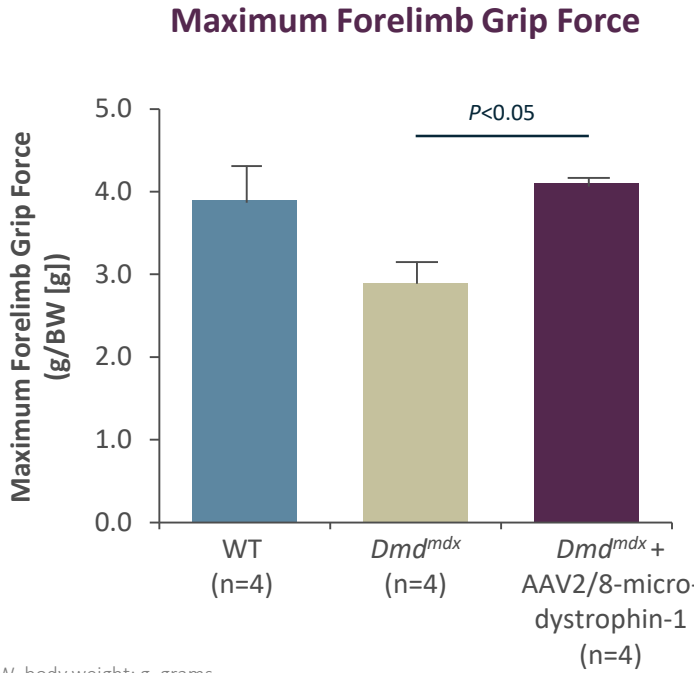
Unpublished data from the laboratory of Serge Braun.

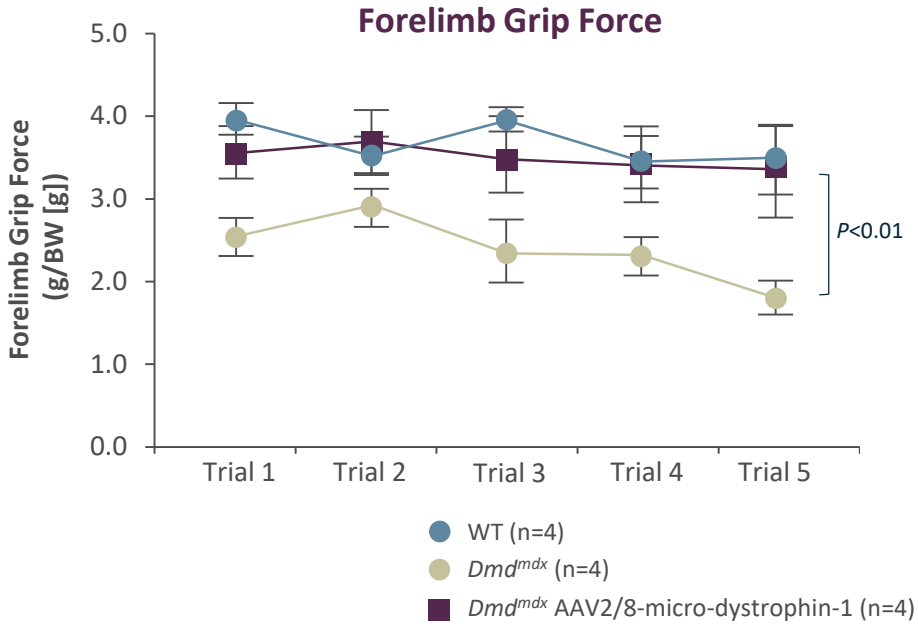
Improved Cardiac Function in *Dmd*^{mdx} Subjects Treated With AAV2/8-Micro-dystrophin-1



IVRT, isovolumic relaxation time; mm, millimeter; msec, millisecond.
Larcher T, et al. *PLoS One*. 2014;9(10):e110371.

Improved Force Grip Response in *Dmd*^{mdx} Subjects Treated With AAV2/8-Micro-dystrophin-1 (3.5 months postinjection)





BW, body weight; g, grams.
Unpublished data from the laboratory of Serge Braun.

Preclinical Studies of AAV2/8-Micro-dystrophin-1 in the GRMD Model

SAREPTA THERAPEUTICS

GENETHON
CURE THROUGH INNOVATION

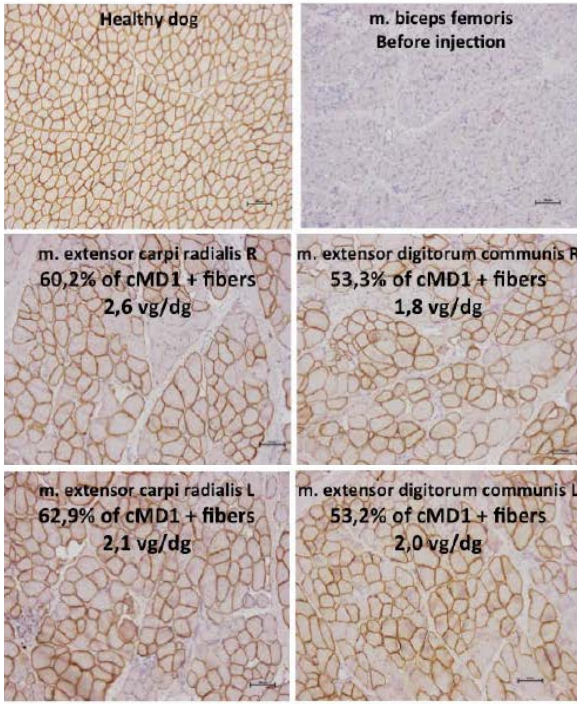
Durable Response Observed in GRMD Subjects Treated With High-dose AAV2/8-Micro-dystrophin-1

Dose	Timing of Follow-up	Subject	Age at Injection	Follow-up Duration After Injection
High (1×10^{14} vg/kg)	Long term	IV 1	2.0 months	24.0 months
		IV 2	2.5 months	***>4 years***
	8 months postinjection	IV 3	2.0 months	7.5 months
		IV 4	2.0 months	8.5 months
		IV 5	2.5 months	8.0 months
Low (2×10^{13} vg/kg)	8 months postinjection	IV 6	2.0 months	8.5 months
		IV 7	2.0 months	8.5 months
		IV 8	2.5 months	6.5 months

IV, intravenous.

Le Guiner C, et al. *Nat Commun*. 2017;8:16105.

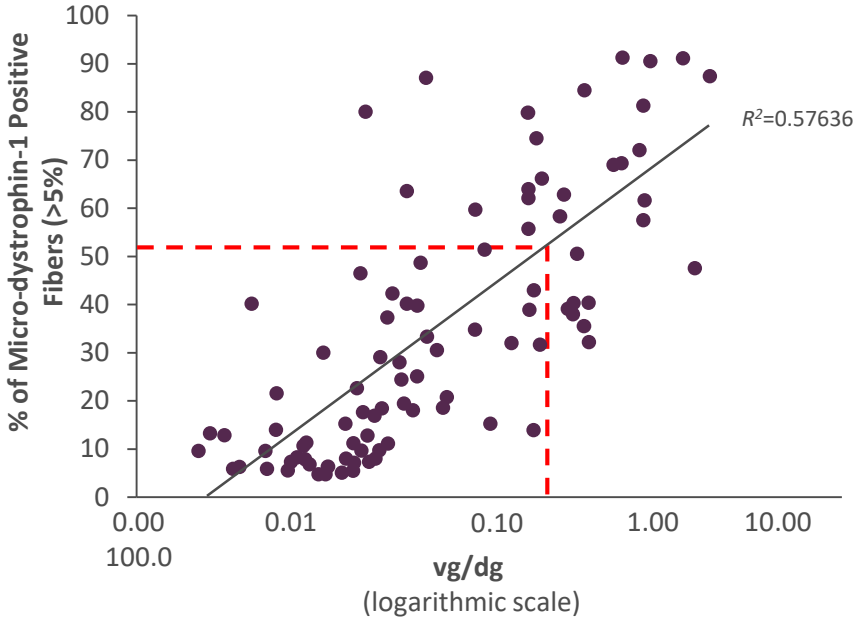
Sustained Levels of Dystrophin Expression Are Observed in GRMD Subjects 27 Months After a Single Injection of High-dose AAV2/8-Micro-dystrophin-1



Muscle Sample	Micro-dystrophin-positive Fibers	Vector Genomes/ Diploid Genomes*
Healthy dog	NA	NA
m biceps femoris (Bef inj)	NA	NA
m extensor carpi radialis, R	60%	2.6
m extensor carpi radialis, L	63%	2.1
m extensor digitorum communis, R	53%	1.8
m extensor digitorum communis, L	53%	2.0

*Diploid genomes refers to the GRMD subject DNA.
Bef inj, before injection; L, left; m, muscle; NA, not applicable; R, right.
Le Guiner C, et al. *Nat Commun*. 2017;8:16105.

Levels of AAV2/8-Micro-dystrophin-1 Found in Target Tissue Are Positively Associated With the Percentage of Micro-dystrophin-Positive Fibers

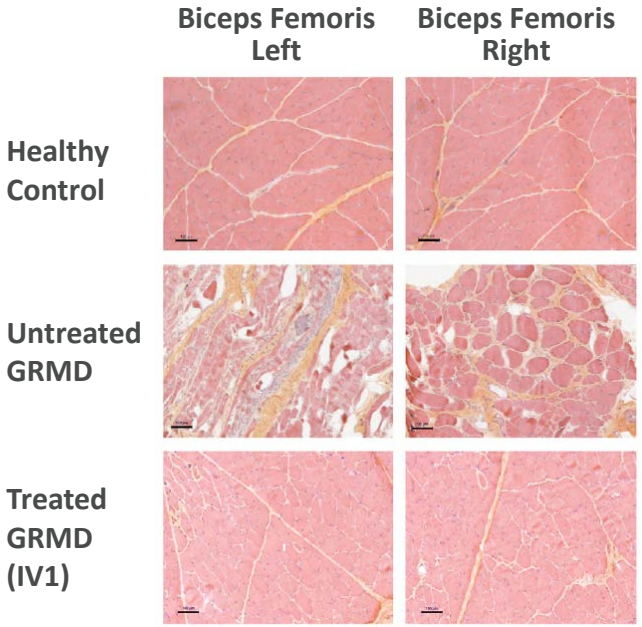


- 1 vg/dg translates to ~50% micro-dystrophin-positive fibers

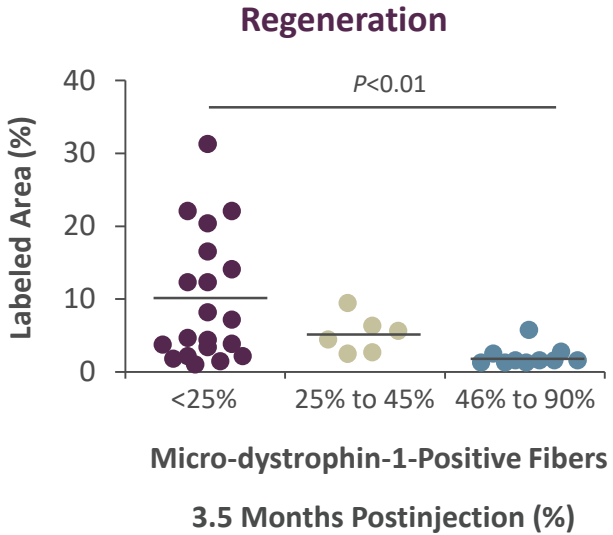
Le Guiner C, et al. *Nat Commun*. 2017;8:16105.

Improved Pathologic Pattern in GRMD Subjects Treated With AAV2/8-Micro-dystrophin-1

Histopathology



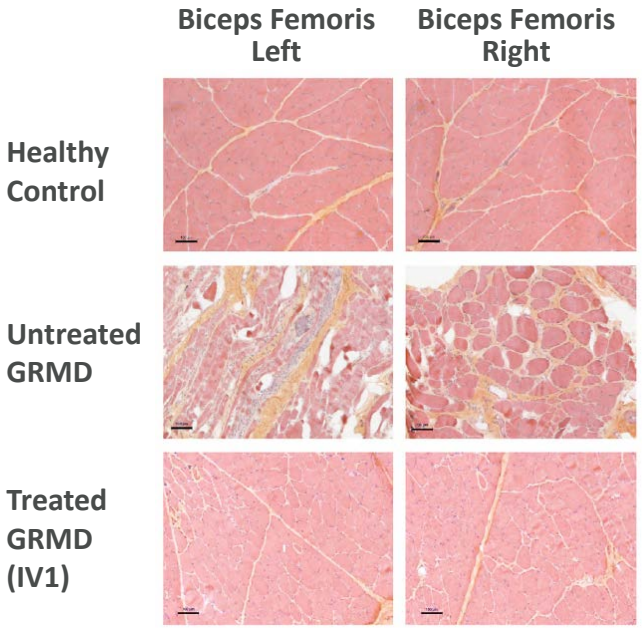
Greater Percentages of Micro-dystrophin-Positive Fibers Are Associated With Less Myofiber Regeneration



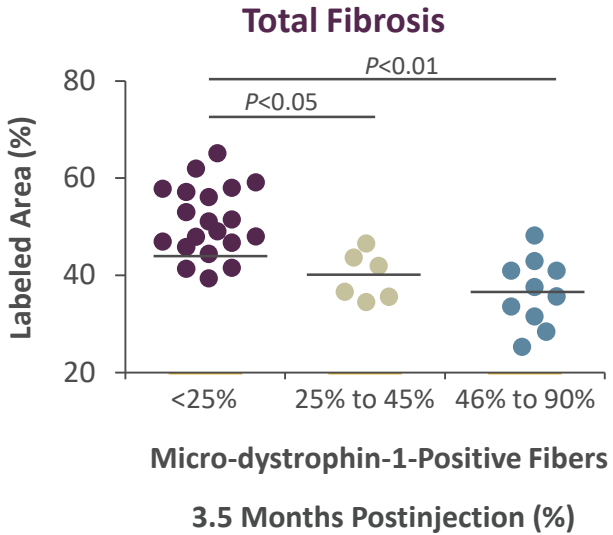
Le Guiner C, et al. *Nat Commun*. 2017;8:16105.

Improved Pathologic Pattern in GRMD Subjects Treated With AAV2/8-Micro-dystrophin-1

Histopathology



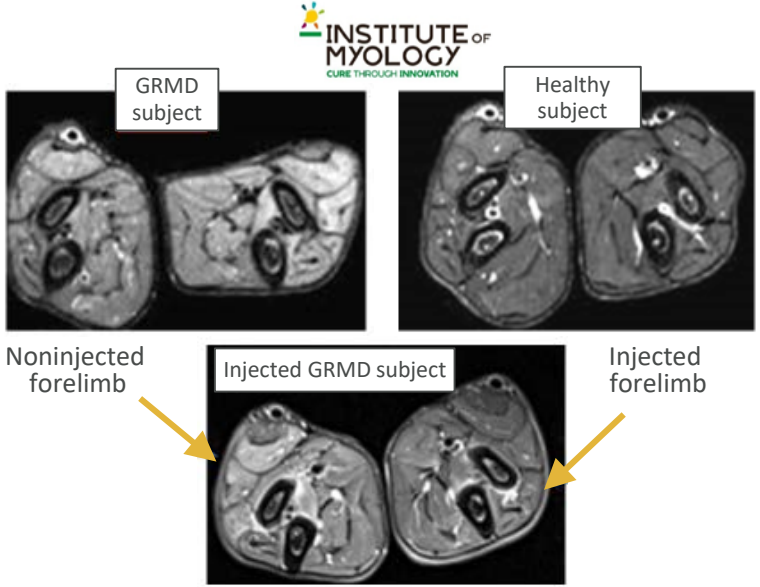
Greater Percentages of Micro-dystrophin-Positive Fibers Are Associated With Less Total Fibrosis



Le Guiner C, et al. *Nat Commun*. 2017;8:16105.

Improved ^{1}H-NMR Parameters in GRMD Subjects Treated With AAV2/8-Micro-dystrophin-1

Much Improved ^{1}H-NMR Parameters

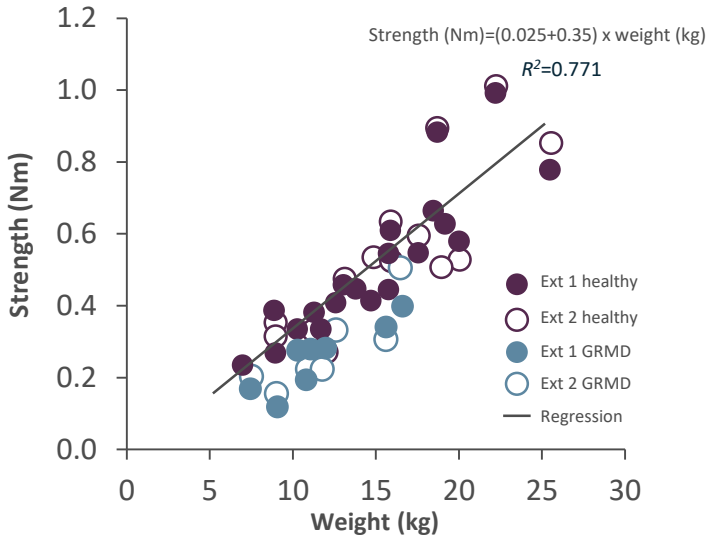


- Reduction of
  - Edema
  - Inflammation
  - Necrosis
  - Cell damage
- More homogeneous and decreased muscle intensity in injected forelimb vs noninjected forelimb

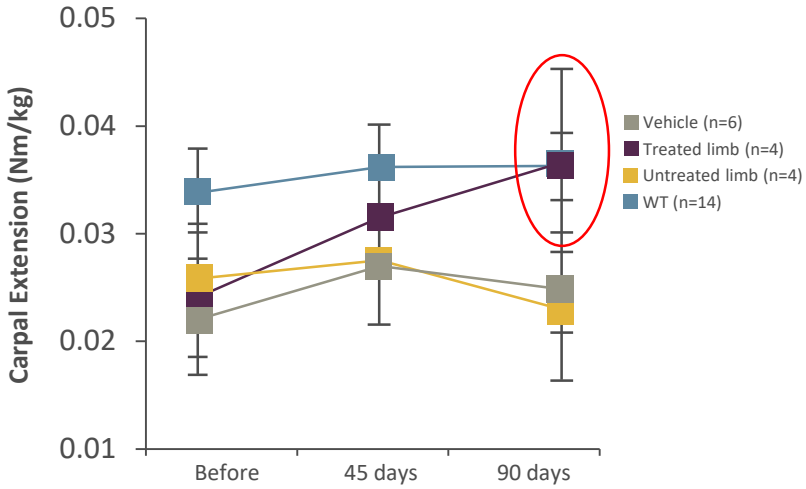
^{1}H-NMR, proton nuclear magnetic resonance.
Le Guiner C, et al. *Nat Commun.* 2017;8:16105.

Improved Muscle Strength in GRMD Subjects Treated With AAV2/8-Micro-dystrophin-1

Strength Is Proportional to Weight in Both Healthy and GRMD Subjects



Improved Muscle Extension Strength



- Significantly improved muscle extension strength in the injected forelimbs vs noninjected limbs, and vs untreated GRMD subjects
- Muscle strength improves from Day 45 to Day 90

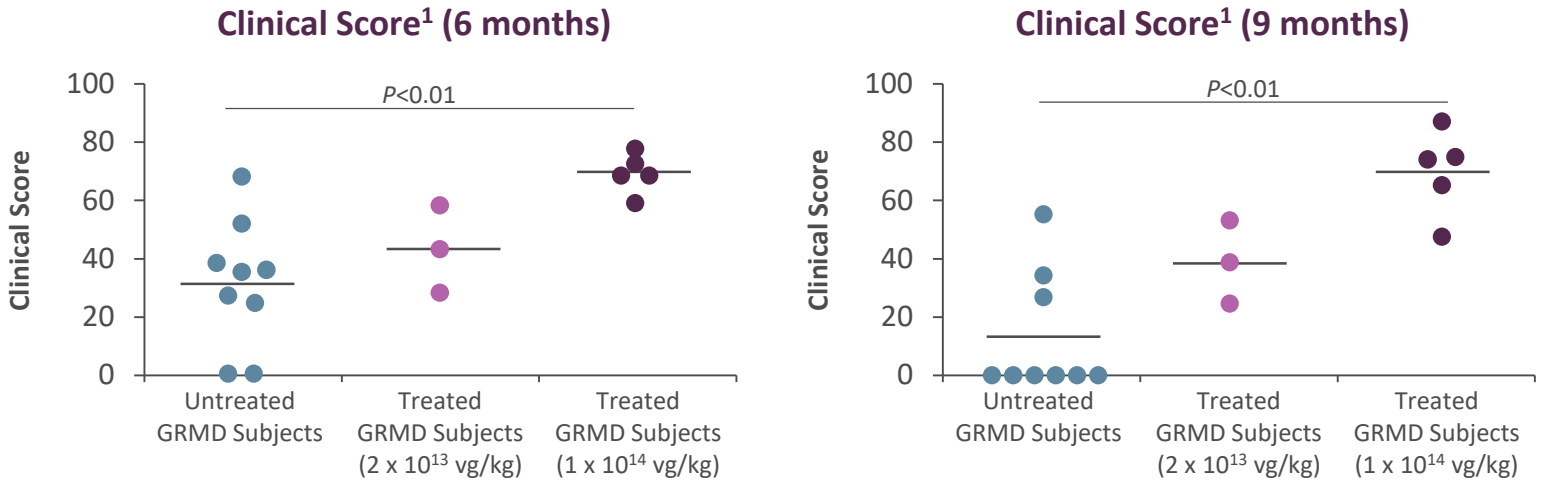
Figures adapted with permission from Le Guiner C, et al.

Nm, newtons per meter (torque).

Le Guiner C, et al. *Nat Commun.* 2017;8:16105.

Improved Clinical Scores in GRMD Subjects Treated With AAV2/8-Micro-dystrophin-1[1]

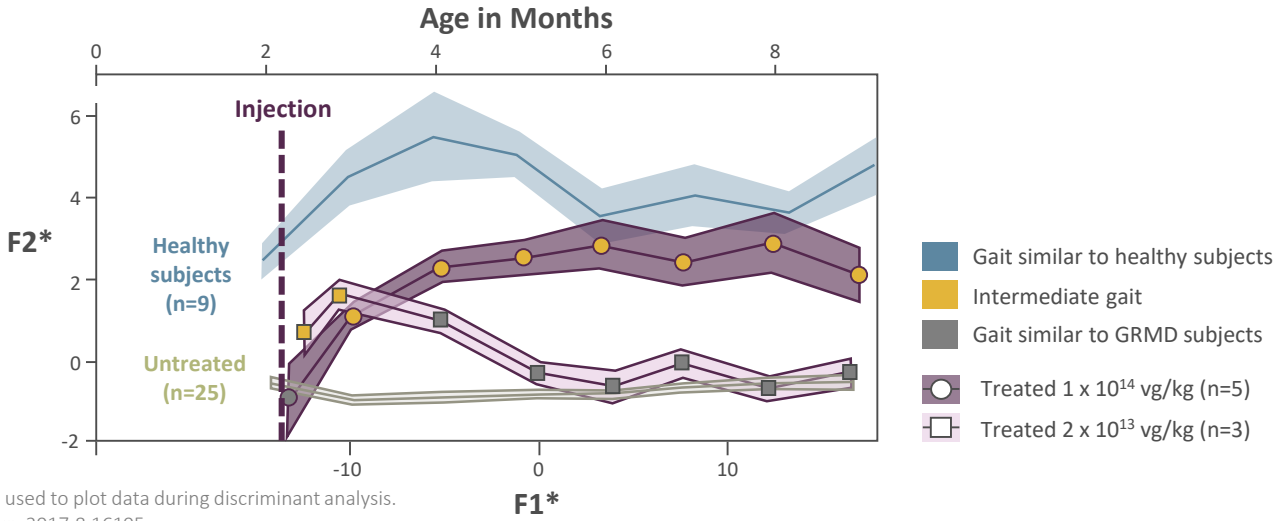
- Weekly clinical exams[2]
  - Scoring of different criteria, eg, dysphagia, breathing, muscular firmness, general activity
  - 100% = healthy subjects



1. Le Guiner C, et al. *Nat Commun*. 2017;8:16105.
2. Rouger K, et al. *Am J Pathol*. 2011;179(5):2501-2518.

Improved Gait Quality of GRMD Subjects Treated With AAV2/8-Micro-dystrophin-1[1]

- Bimonthly gait evaluation using Locométrix® device[2,3]
  - Accelerometry in 3 axes: dorsoventral, mediolateral, craniocaudal
  - Global gait index: canonical discriminant analysis (8 factors)

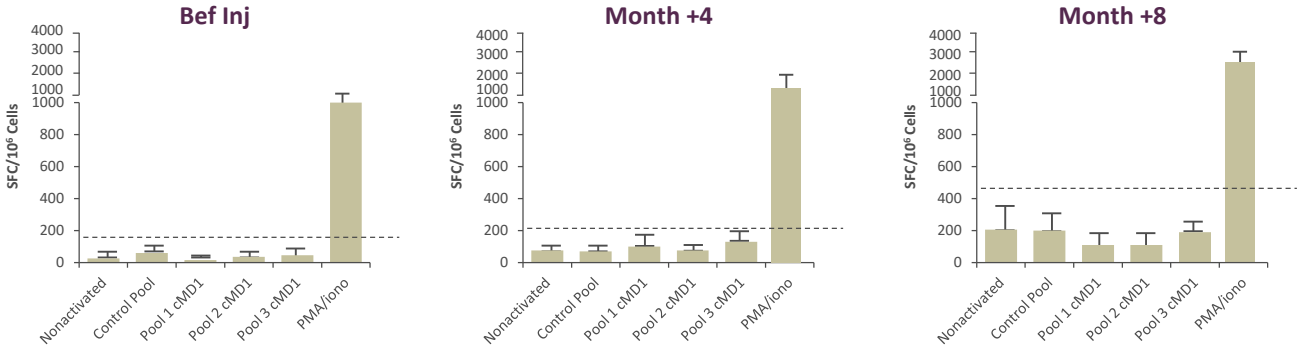


*F1 and F2 represent the 2 axes used to plot data during discriminant analysis.

1. Le Guiner C, et al. *Nat Commun*. 2017;8:16105.
2. Barthélémy I, et al. *BMC Musculoskelet Disord*. 2011;12:75.
3. Barthélémy I, et al. *Neuromuscul Disord*. 2009;19(11):788-796.

No Adverse Cellular Immune Responses to Micro-dystrophin-1 or to AAV Capsid

IFNγ ELISPOT (Cellular Immunity)



Transient antibody response to micro-dystrophin (without apparent consequences)

Group	Dog	Humoral Immunity (circulating anti-cMD1 IgG [Western immunoblot])						Cellular Immunity (IFNγ secretion by PBMC with cMD1 peptides [ELISPOT])								
		Bef Inj	Mo +1	Mo +2	Mo +3	Mo +4	Mo +8	Bef Inj	Mo +1	Mo +2	Mo +3	Mo +4	Mo +5	Mo +6	Mo +7	Mo +8
Group IV-A 1×10^{14} vg/kg	IV1	–	–	++	–	–	–	–	–	–	–	–	–	–	–	–
	IV2	–	+	+++	++	+	–	–	–	–	–	–	–	–	–	–
	IV3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	IV4	–	–	++	–	–	–	–	–	–	–	–	–	–	–	–
	IV5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Group IV-B 2×10^{13} vg/kg	IV6	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	IV7	–	–	–	–	–	–	–	–	–	–	–	—	–	–	–
	IV8	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

+, detection of circulating anti-cMD1 IgG antibodies; –, no detection of circulating anti-cMD1 IgG antibodies or no detection of IFNγ secretion by PBMCs; ELISPOT, enzyme-linked immunospot; IFNγ, interferon gamma; IgG, immunoglobulin G; Mo, month; PBMC, peripheral blood mononuclear cell; PMA, phorbol ester; SFC, spot-forming cells.

Le Guiner C, et al. *Nat Commun.* 2017;8:16105.

Improved Clinical Status of GRMD Subjects Injected With AAV2/8-Micro-dystrophin-1 (video)

Video courtesy of Généthon.

Summary

- AAV2/8-micro-dystrophin-1 is safe and therapeutic in preclinical models
  - Widespread expression of micro-dystrophin in *mdx, Dmd*^{mdx}, and GRMD preclinical models
  - Expression is sustained and rescues skeletal and heart muscle structure and function in *mdx* subjects, *Dmd*^{mdx} subjects, and a GRMD model up to 32 months postinjection
  - Injection of AAV2/8-micro-dystrophin-1 caused no cytotoxic immune response to the transgene product or to the AAV capsid
  - Prolongation of survival in GRMD subjects (>2 years, n=2 subjects: >4 years, n=1)
  - Improvement of clinical parameters and pathology
  - Minimal efficacious dose appears to be >3 x 10^{13} vg/kg
- **Ongoing**
  - Preclinical dose study in *Dmd*^{mdx} subjects
  - GMP large (400 L)-scale production

YPOSKESI

Break

OUR VISION FOR THE FUTURE OF

Precision Genetic Medicine

SAREPTA THERAPEUTICS, INC. 2018 R&D DAY

Systemic Delivery of AAVrh74.MHCK7.Micro-dystrophin for DMD

Jerry Mendell, MD
Center for Gene Therapy
Nationwide Children's Hospital
Columbus, OH

Louise Rodino-Klapac, PhD
Sarepta Therapeutics
Cambridge, MA

SAREPTA THERAPEUTICS

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.

Today's Presentation

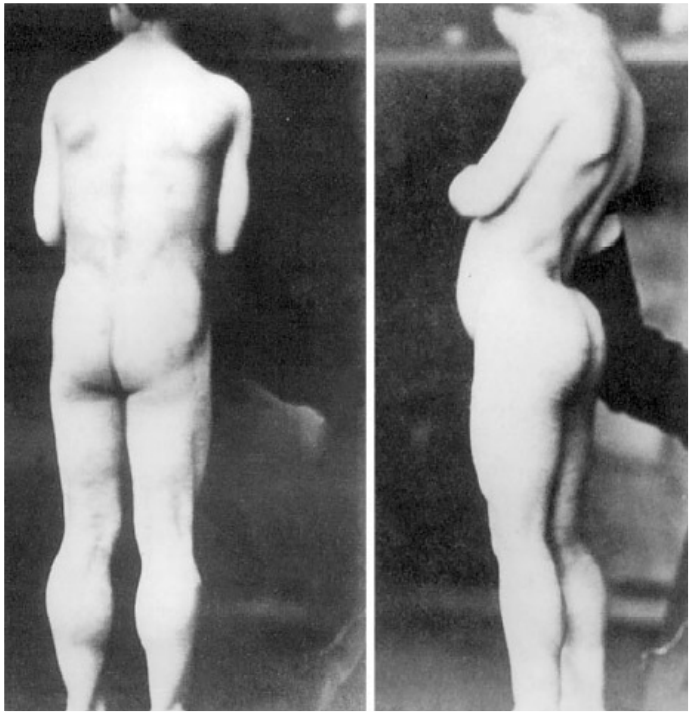
- DMD background and the engineering of micro-dystrophin
- Micro-dystrophin preclinical data
- Evidence of gene therapy efficacy from SMA
- Clinical data of micro-dystrophin gene therapy for DMD

DMD, Duchenne muscular dystrophy; SMA, spinal muscular atrophy.

DMD
Our motivation

- Most common life-threatening childhood muscular dystrophy
- Devastating disease
  - Boys are wheelchair-dependent by 12-13 years old
- Patients die in early 20s-30s from pneumonia and/or cardiomyopathy
- Incidence of 1:3500–5000 male births worldwide
- Elevated CK levels

Picture of DMD patient taken by Duchenne (1863)



CK, creatine kinase.

Dystrophin-associated Protein Complex (DAPC)

- Dystrophin is a core component of the DAPC
- Functions as a “shock absorber” during muscle contraction
- Loss of dystrophin causes disassembly of the entire DAPC
- Normal muscle contraction in DMD causes chronic muscle breakdown
- ***Restore the DAPC complex – restore function***

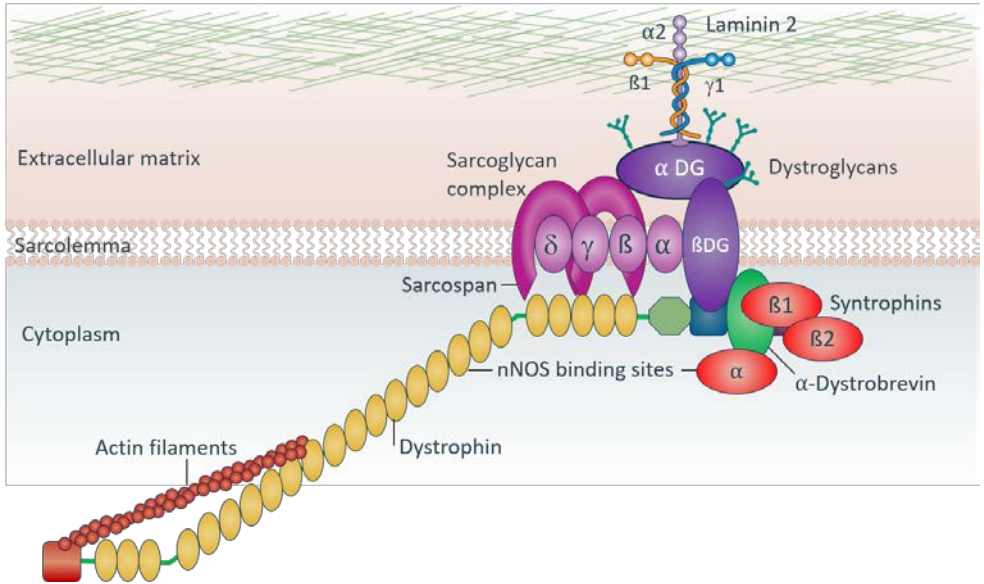
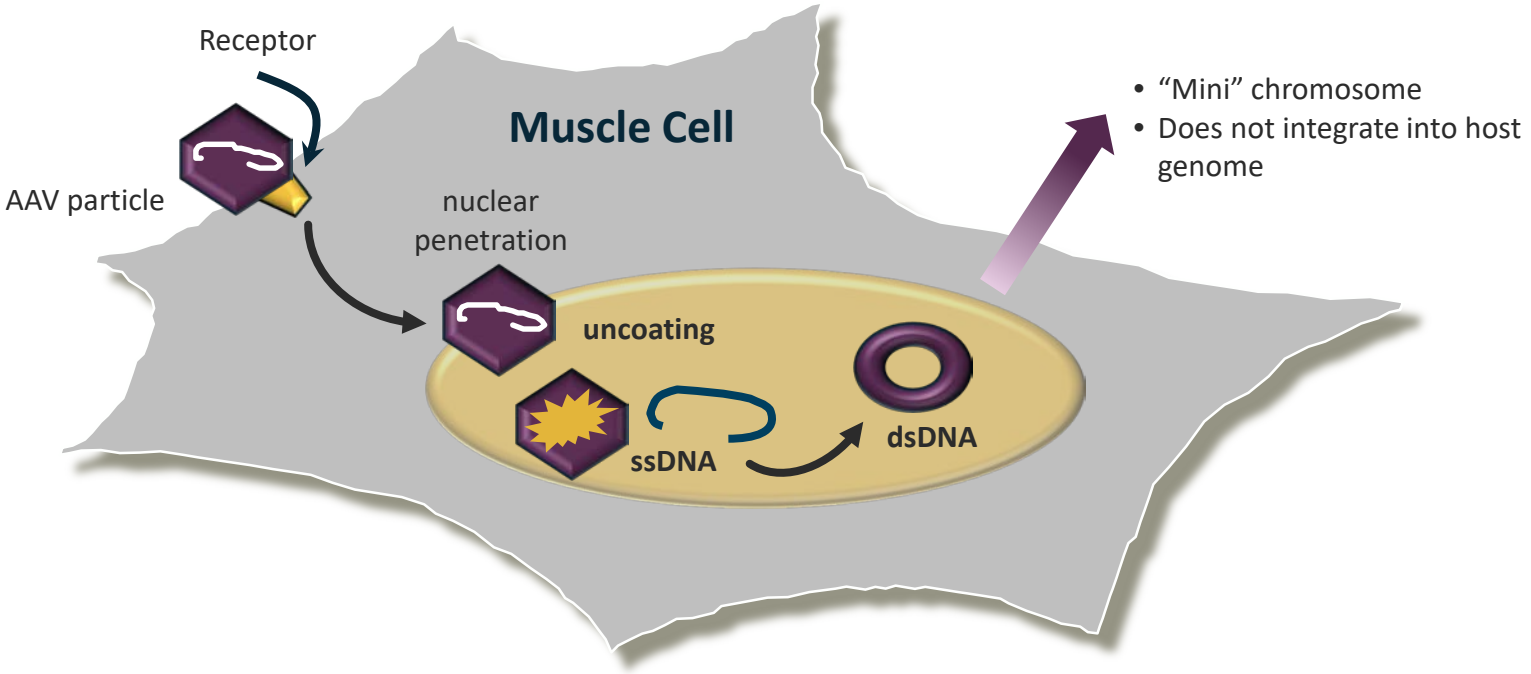


Image adapted from Fairclough RJ, et al. *Nat Rev Genet*. 2013;14(6):373-378.

DG, dystroglycan; nNOS, neuronal nitric oxide synthase.

Adeno-associated Virus (AAV) Is a Delivery Vehicle for Dystrophin

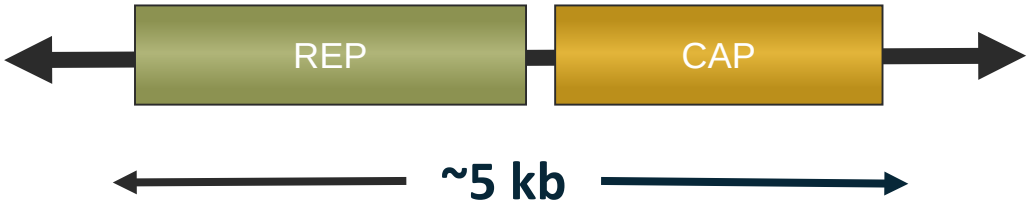


DNA, deoxyribonucleic acid; dsDNA, double-stranded DNA; ssDNA, single-stranded DNA.

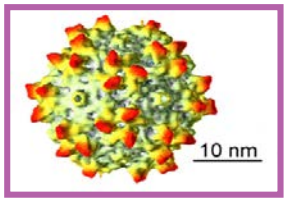
Adeno-associated Virus (AAV) Is a Delivery Vehicle for Dystrophin

- ssDNA virus
- Does not cause disease in humans
- Long-term persistence in cells

Open reading frames of AAV



AAV Capsid

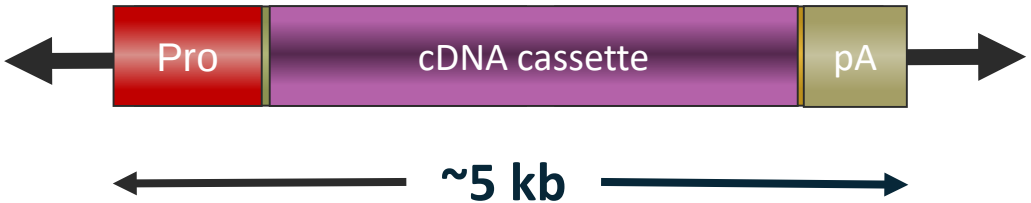


kb, kilobase; nm, nanometer.

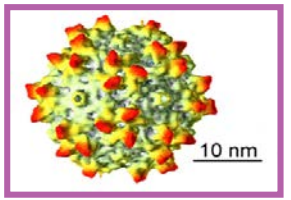
Adeno-associated Virus (AAV) Is a Delivery Vehicle for Dystrophin

- ssDNA virus
- Does not cause disease in humans
- Long-term persistence in cells
- Gene therapy requires replacement of viral genes with gene of interest

Structure of typical AAV construct with gene of interest



AAV Capsid

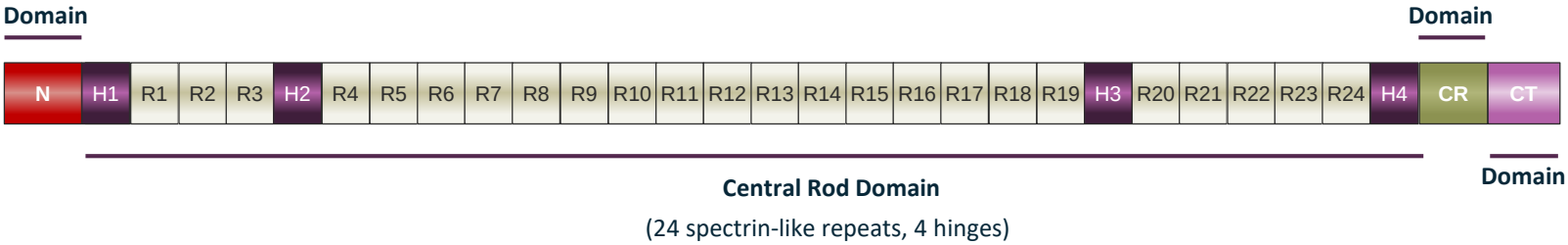


cDNA, complementary DNA; kb, kilobase; pA, polyadenylation signal; nm, nanometer; Pro, promoter sequence.

Pathogenesis of DMD

- Dystrophin is the largest gene in the human genome at 2.6 Mb
  - Poses a critical obstacle for molecular manipulation

Dystrophin encodes a protein with 4 domains



CR, cysteine-rich; CT, carboxy-terminal; H, hinge; Mb, megabase; N, amino-terminal; R, spectrin-like repeat.

How Do We Decrease the Size of the *DMD* Gene?

Birth of the mini-dystrophins

- Clinical observations paved the way for mini-gene therapy
- 61-year-old ambulatory patient with Becker muscular dystrophy had 46% of dystrophin coding region deleted (Del 17-48)[1]

***R2** and **R3** critical for force production.*

***R16** and **R17** are required for the association of nNOS with the DAPC. Not present in this patient.*

1. England SB, et al. *Nature*. 1990;343(6254):180-182.
2. Wells DJ, et al. *Hum Mol Genet*. 1995;4(8):1245-1250.

How Do We Decrease the Size of the *DMD* Gene?

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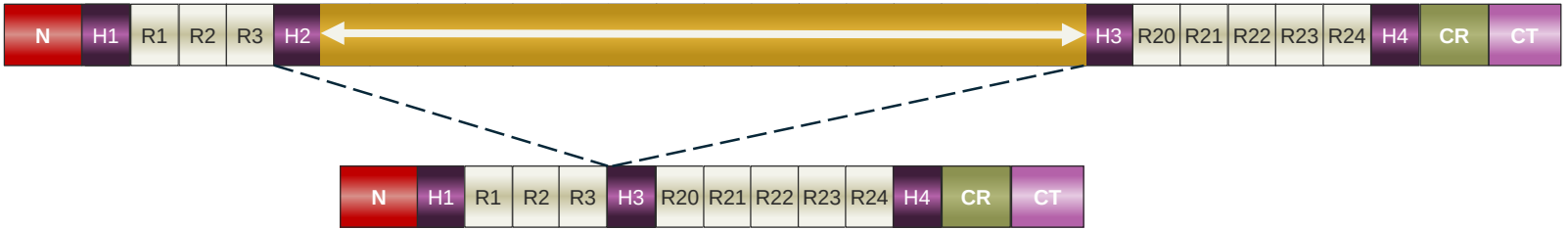

"Mini"-dystrophin[2]
(6 Kb)

***R2** and **R3** critical for force production.*

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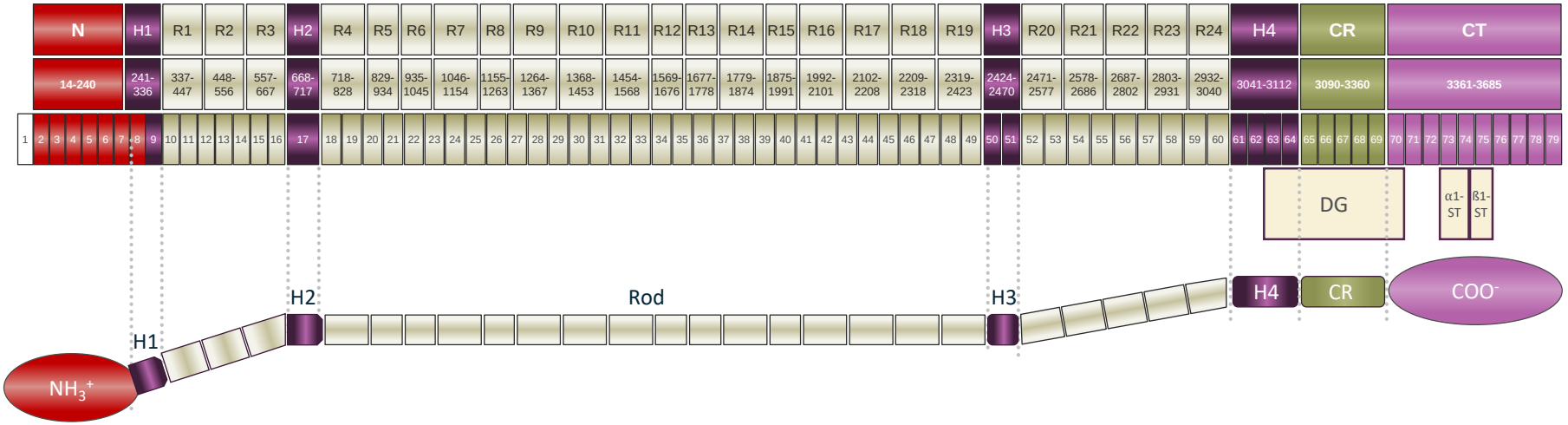
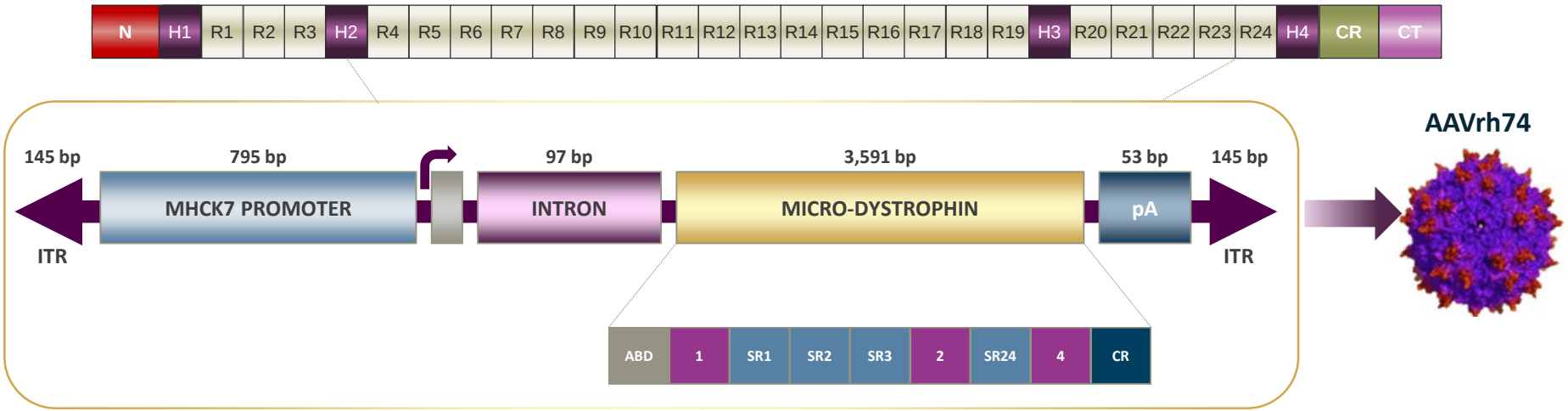
1. England SB, et al. *Nature*. 1990;343(6254):180-182.
2. Wells DJ, et al. *Hum Mol Genet*. 1995;4(8):1245-1250.

Challenge:
Further Modify Dystrophin to <5 Kb So That It Can Fit in AAV Particle



AAVrh74.MHCK7.Micro-dystrophin

- MHCK7 promoter enables robust dystrophin expression in heart and skeletal muscle
- AAVrh74 provides broad distribution to ***all*** muscle types, including the heart and diaphragm



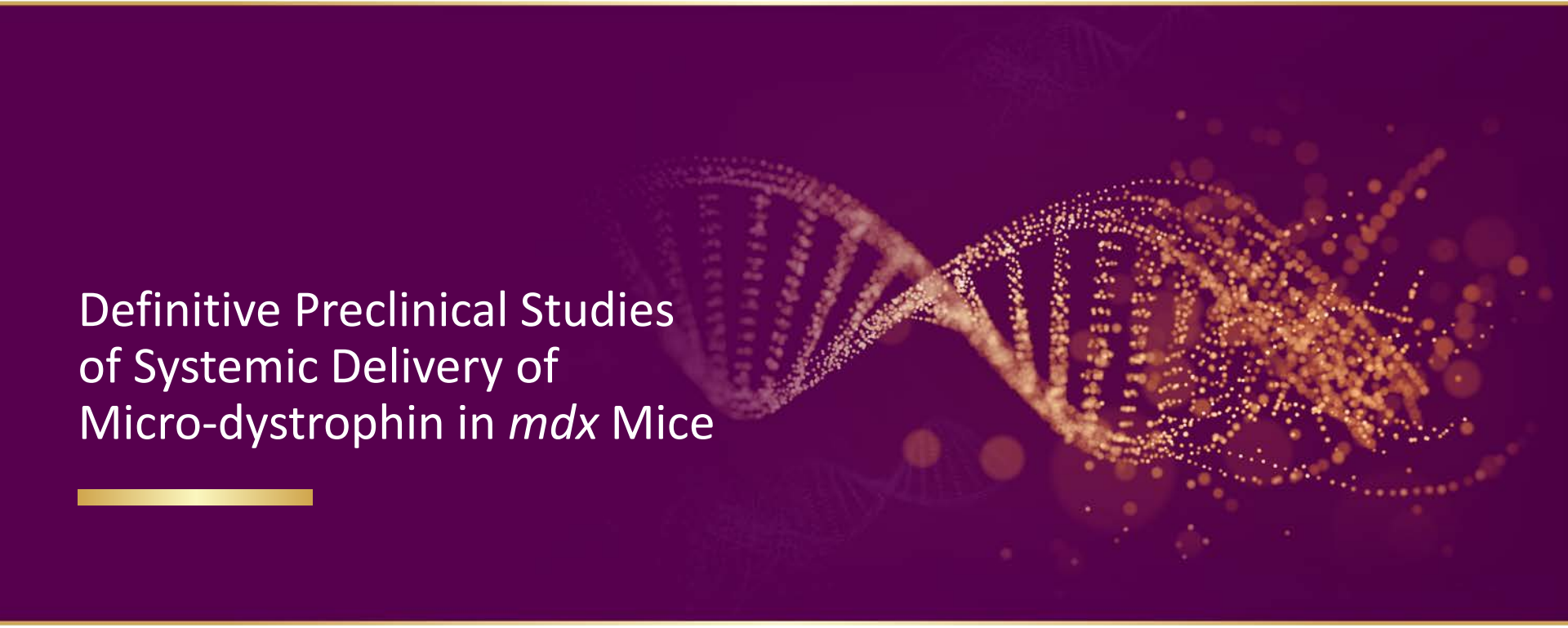
ITR, inverted tandem repeat; SR, spectral-like repeat.

Strong Profile for AAVrh74

- Demonstrated efficacy
  - Ideal systemic biodistribution vs other vectors in preclinical testing
  - Widespread high-level gene expression after IV infusion in preclinical animal models
  - Gene expression in Phase 1 trials across multiple diseases by IM and IV delivery*
  - **Low pre-existing immunogenicity**: Nonhuman serotype guards against pre-existing immunity (still under evaluation; currently <15%)
- Demonstrated safety
  - **No observed adverse effect level (NOAEL)** in primates and mice
    - GLP toxicity studies: IM, n=5; ILP, n=3; IV, n=2
  - **14 human subjects** dosed (IM, n=4; IV, n=10) without vector-related adverse effects
  - **6 approved INDs**

GLP, good laboratory practice; ILP, isolated limb perfusion; IM, intramuscular; IND, investigational new drug; IV, intravenous.
*Unpublished data based on screening of approximately 70 patients with Limb girdle muscular dystrophy (LGMD) or DMD.

Definitive Preclinical Studies of Systemic Delivery of Micro-dystrophin in *mdx* Mice



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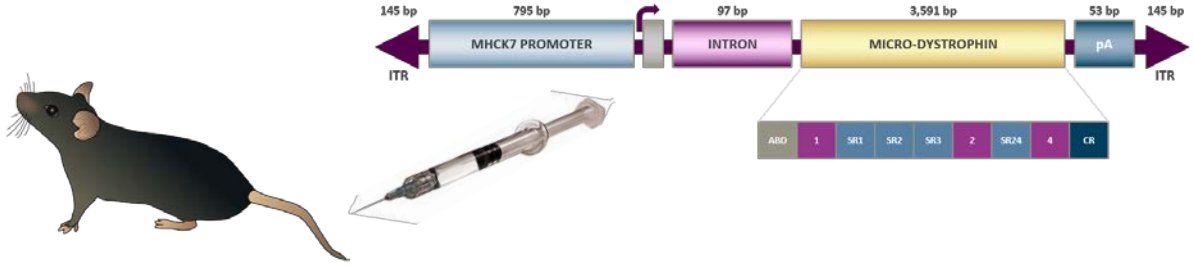
Preclinical IV Study Design for the Delivery of AAVrh74.MHCK7.Micro-dystrophin



2 x 10^{12} vg total dose (8 x 10^{13} vg/kg)

6 x 10^{12} vg total dose (2 x 10^{14} vg/kg)

1.2 x 10^{13} vg total dose (6 x 10^{14} vg/kg)

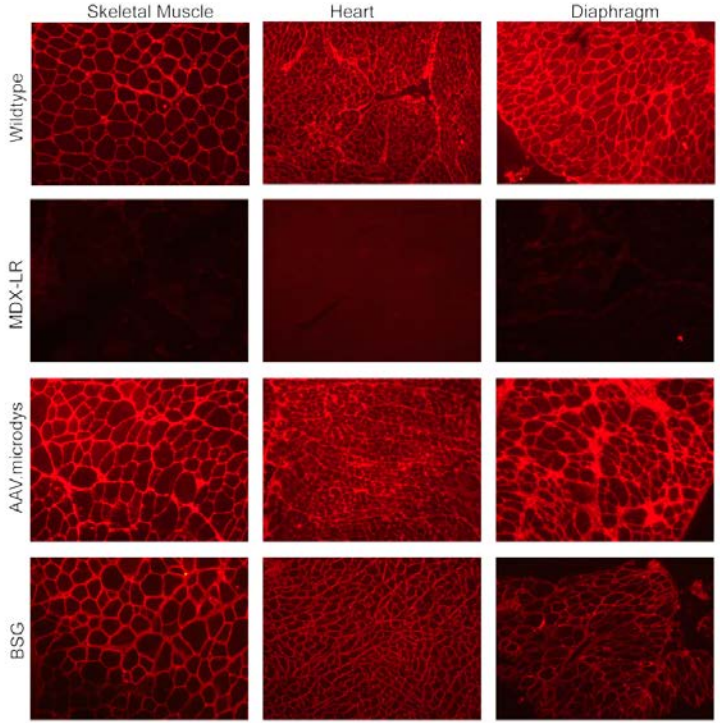
Assess efficacy and safety 12 weeks after gene delivery

- Transgene expression and biodistribution
- Western blot and qPCR
- Histological analysis
- Functional benefit
- Safety and toxicity

qPCR, quantitative polymerase chain reaction; vg, viral genomes.

Reassembly of the Dystrophin-associated Protein Complex With Micro-dystrophin

Dystrophin and BSG Expression (IHC)



BSG, β-sarcoglycan; IHC, immunohistochemistry; LR, locoregional.

Schematic of the DAPC

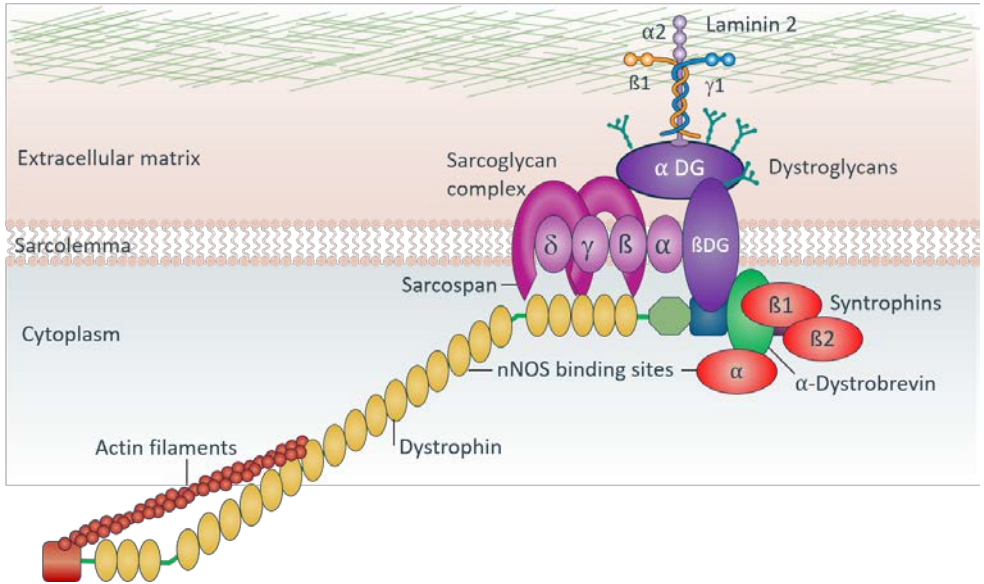
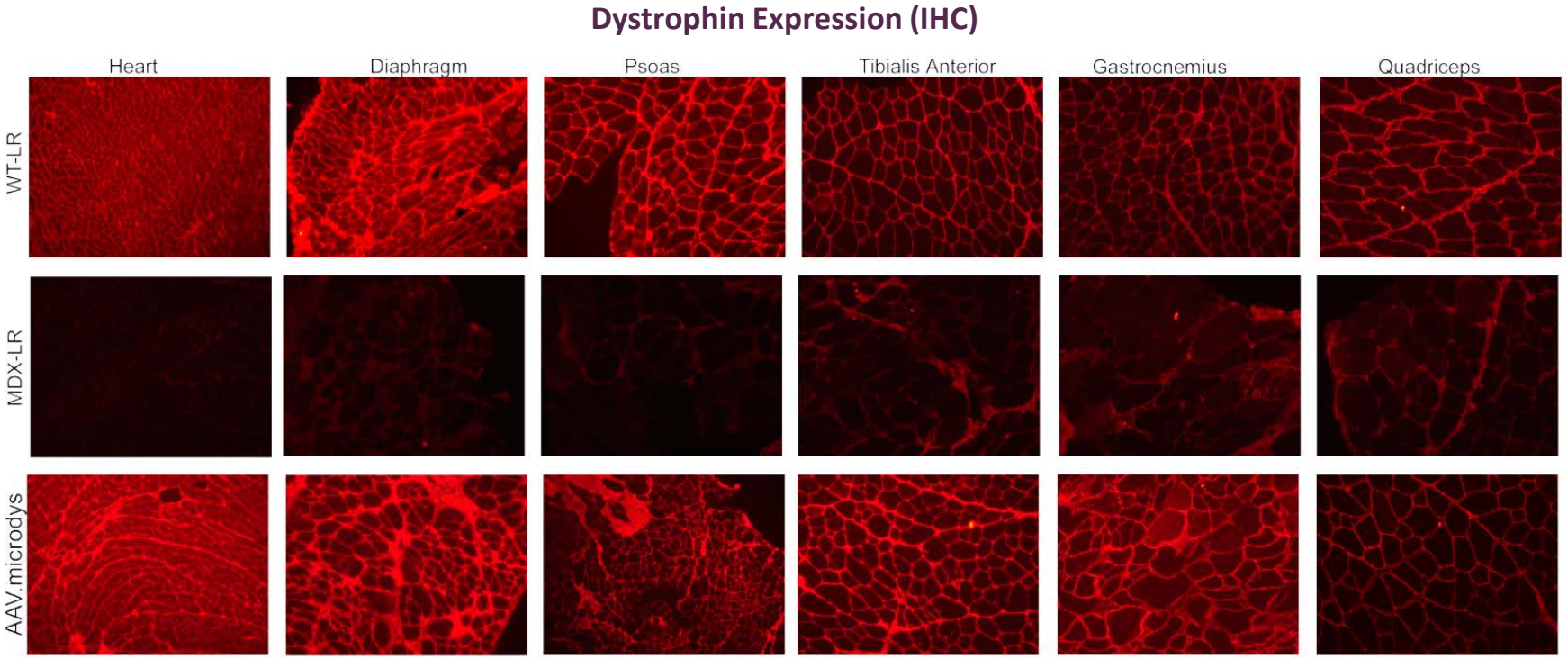


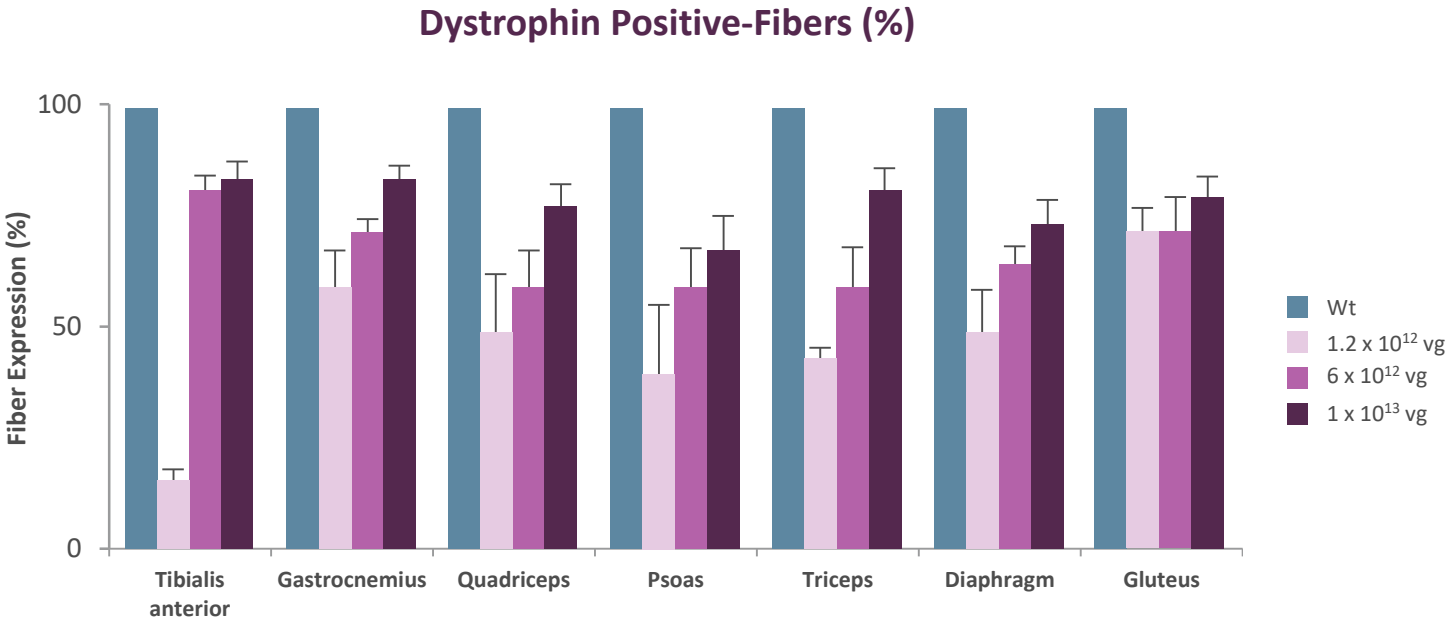
Image adapted from Fairclough RJ, et al. *Nat Rev Genet*. 2013;14(6):373-378.

Widespread Expression After Micro-dystrophin Gene Delivery



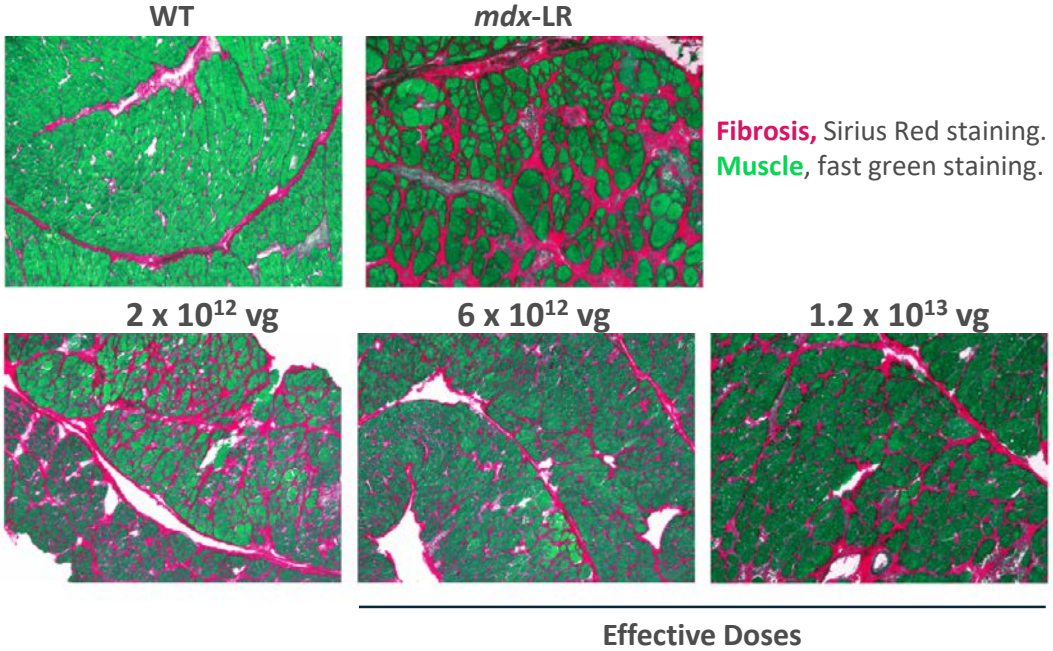
WT, wild-type.

Widespread Expression After Micro-dystrophin Gene Delivery

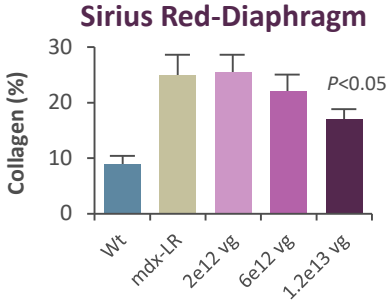


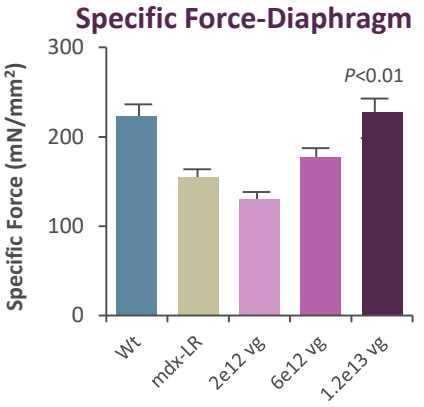
Reduced Fibrosis Accompanies Functional Improvement in the Diaphragm

Evaluation of Fibrosis in the Diaphragm (IHC)



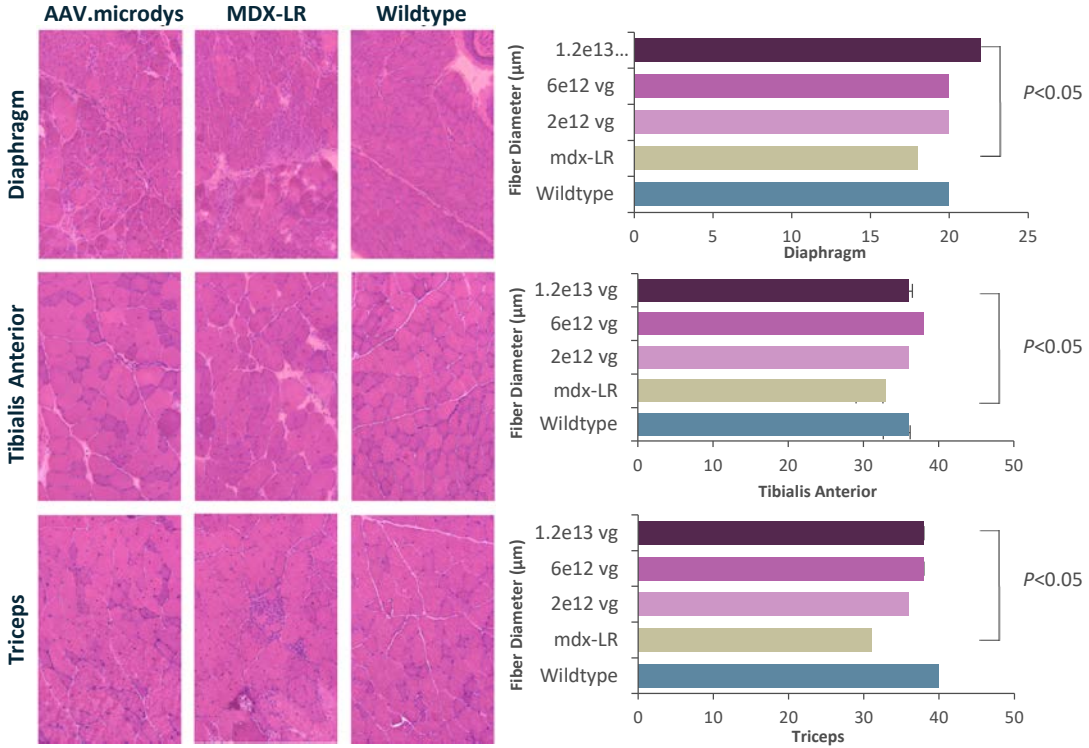
Fibrosis, Sirius Red staining.
Muscle, fast green staining.





mN, milliNewtons.

Histological Improvement in Muscles Treated With AAVrh74.MHCK7.Micro-dystrophin



Pathologist Conclusions

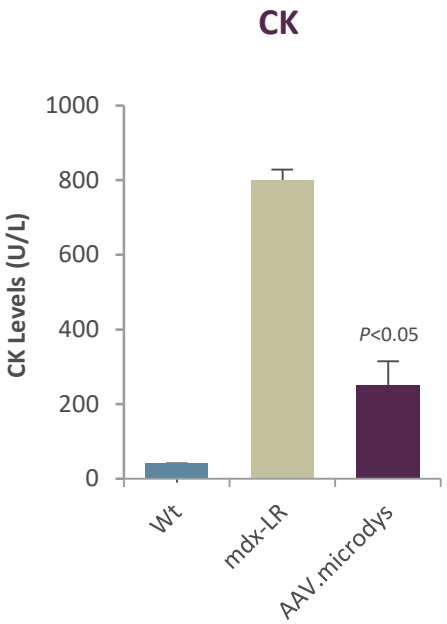
Efficacy

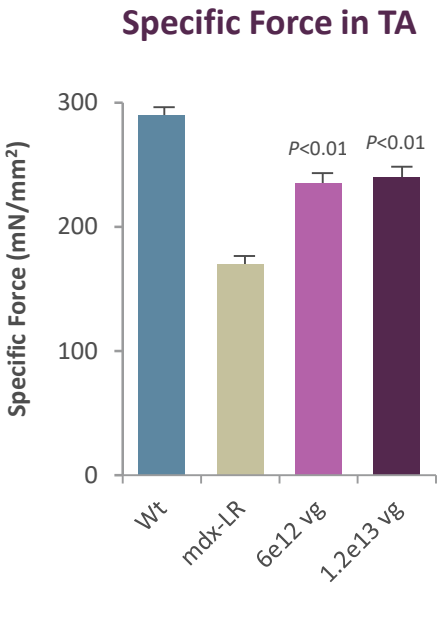
- Injection of *mdx* mice with the test article ***substantially reduced in a dose-dependent manner*** the skeletal myopathy that developed in vehicle-treated, age-matched *mdx* mice

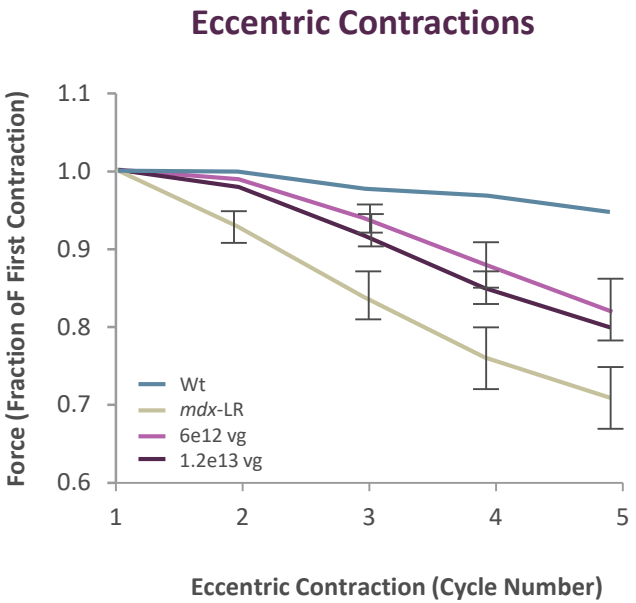
Safety

- The test article AAVrh74.MHCK7.Micro-dystrophin (administered at 2 x 10^{12}, 6 x 10^{12}, or 1.2 x 10^{13} vg total dose by IV injection at 4-6 weeks of age) ***did not induce anatomic lesions*** in muscles of male *mdx* knockout mice at 12 weeks after administration

CK Reduction, Muscle Strength, and Stamina Improvement in *mdx* Mice Treated With AAVrh74.MHCK7.Micro-dystrophin

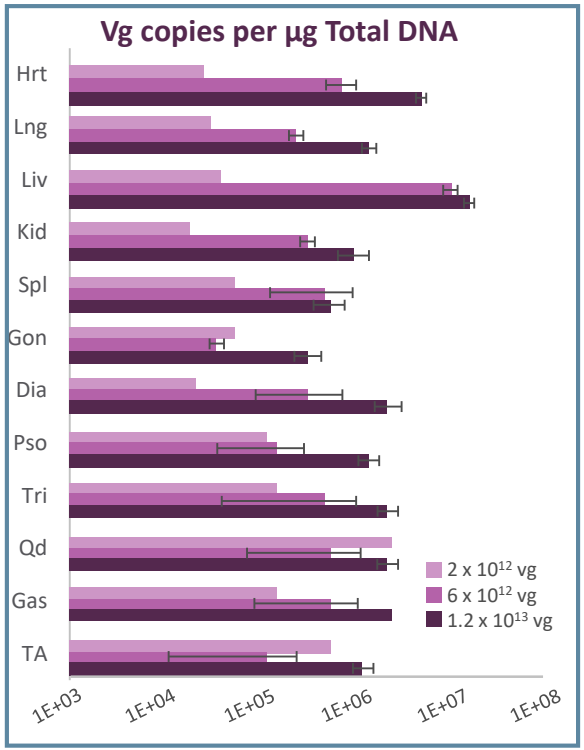


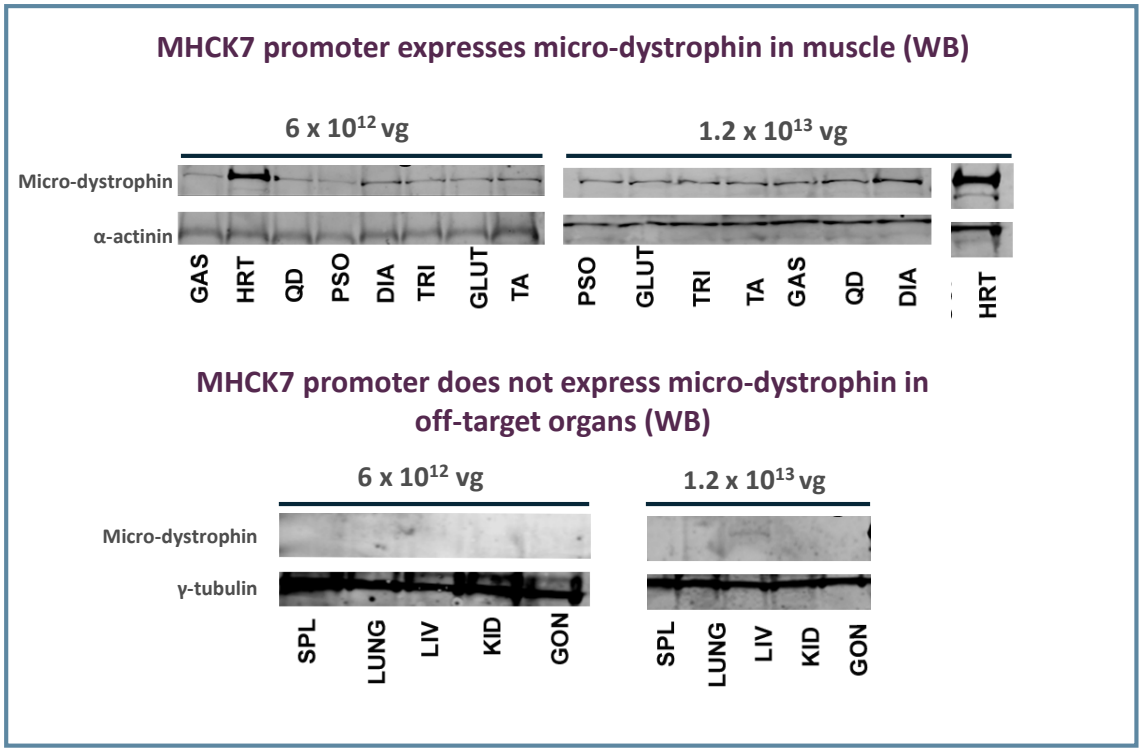




- No difference in fatigue in the 6 x 10^{12} vg and 1.2 x 10^{13} vg doses

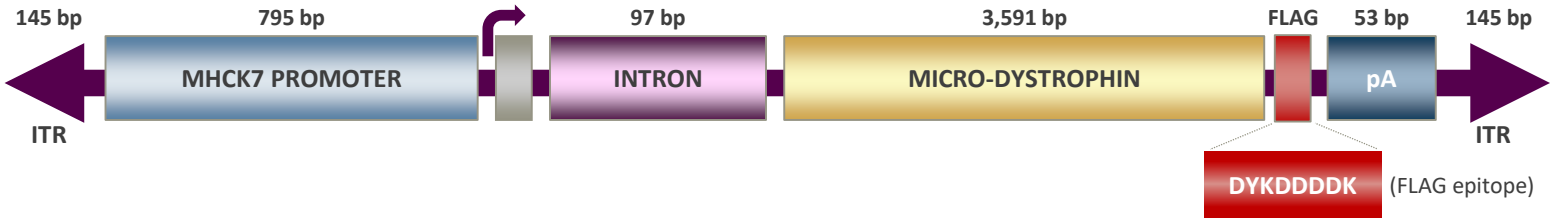
Widespread Biodistribution Throughout 8 Different Muscle Groups With Systemic Delivery of Micro-dystrophin in the *mdx* Mouse Model



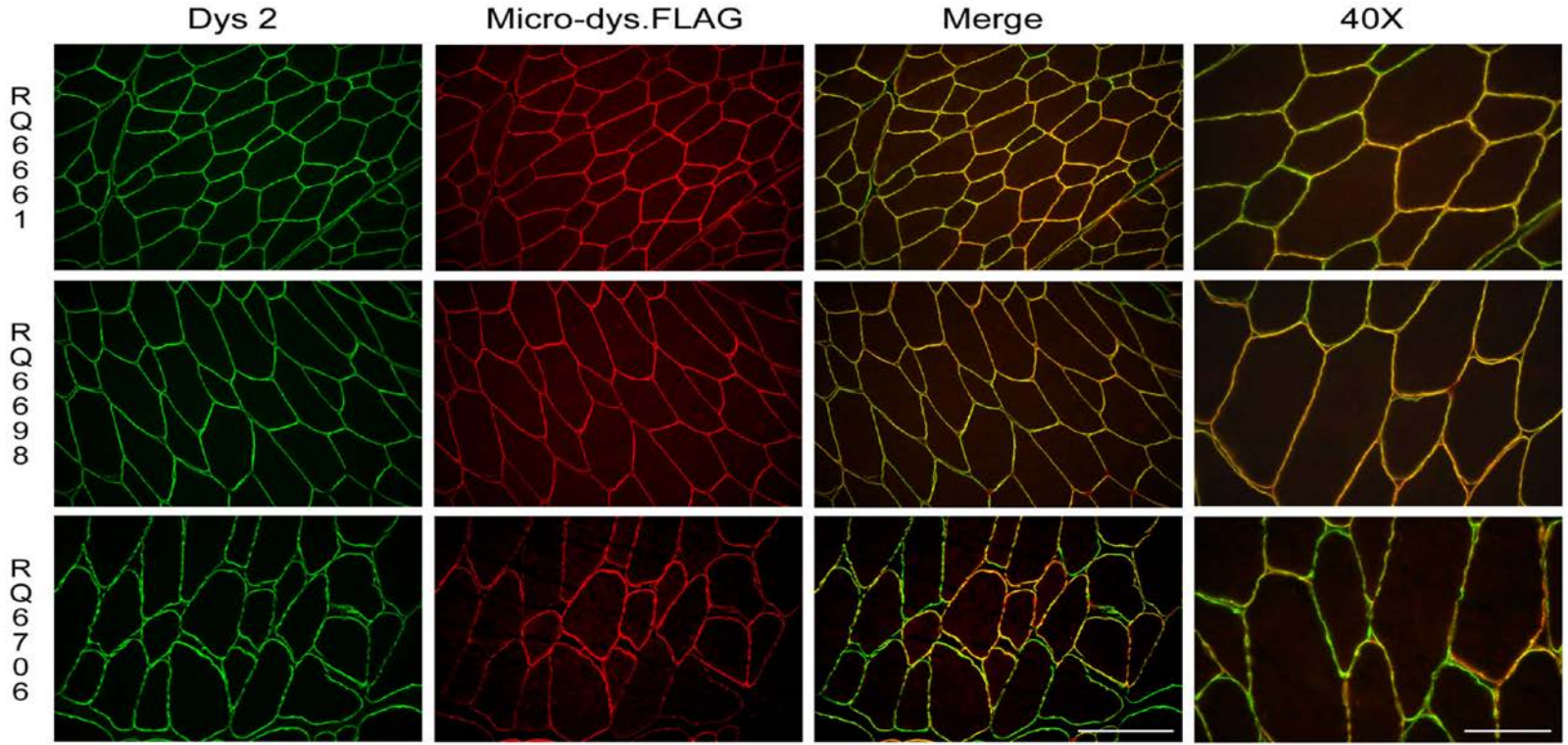


Dia, diaphragm; Gas, gastrocnemius, Gon, gonadal; Hrt, heart; kDA, kilodaltons; Kid, kidney; Liv, liver; Lng, lung; Pso, Psoas; Qd, quadriceps; Spl, spleen; Tri, triceps, WB, Western Blot.

Micro-dystrophin With FLAG Tag Will Reveal Transgene Distribution in Nonhuman Primates (NHPs)

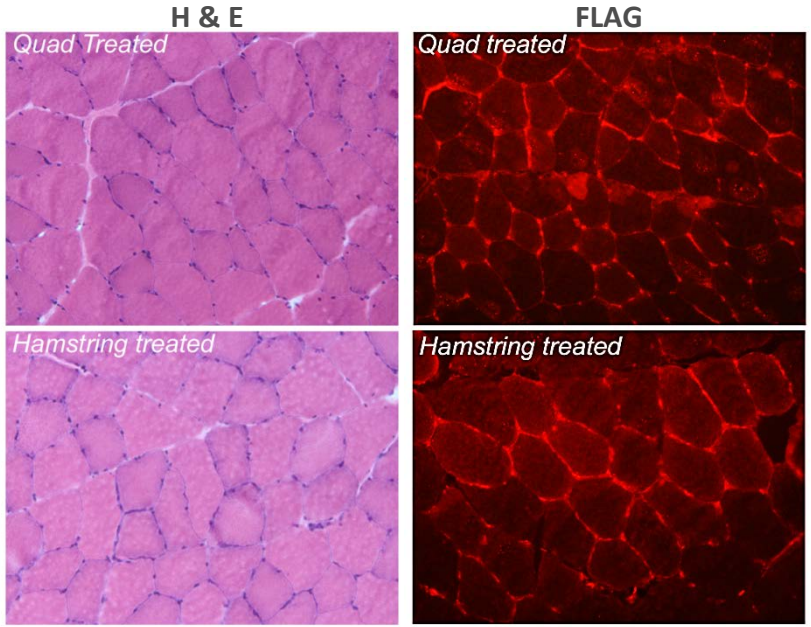


Endogenous Dystrophin and Micro-dystrophin.FLAG Colocalize to the Sarcolemma in NHPs

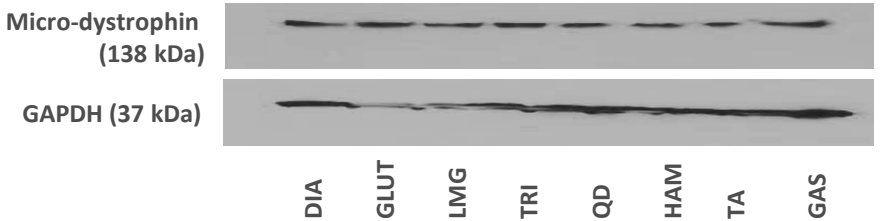


Widespread Biodistribution With Systemic Delivery of Micro-dystrophin in NHPs

Micro-dystrophin Tissue Expression (IHC)



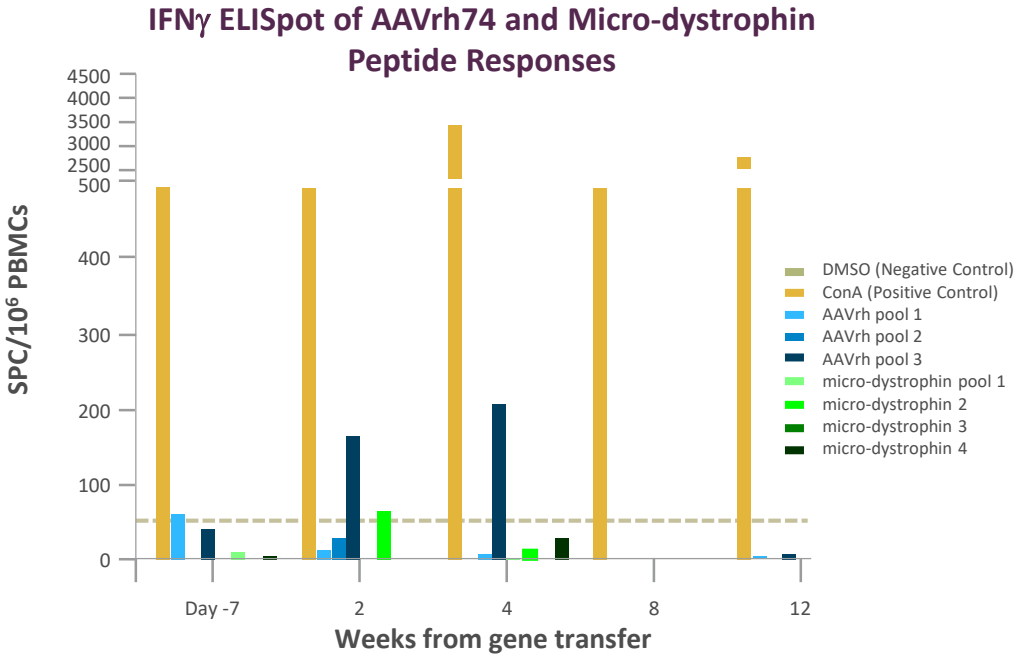
Micro-dystrophin Tissue Expression (WB)

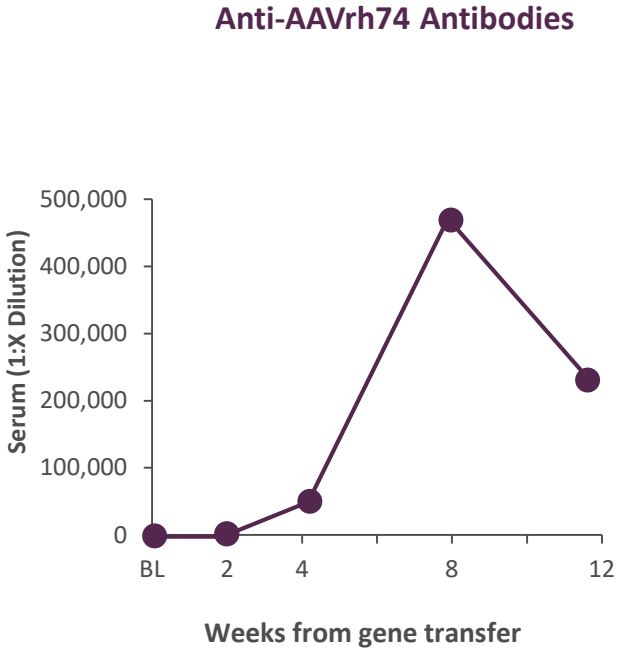


- NHPs were treated with 2 x 10^{14} vg/kg with AAVrh74.MHCK7.Micro-dystrophin

GAPDH, glyceraldehyde 3-phosphate dehydrogenase; H & E, hematoxylin and eosin; HAM, hamstring; LMG, left adductor magnus.

No Abnormal Immunological Responses Were Observed With Systemic Delivery of Micro-dystrophin in NHPs*†





BL, baseline; CBC, cell blood count; ConA, concanavalin A; ELISpot, enzyme-linked immunospot; DMSO, dimethyl sulfoxide; IFNγ, interferon gamma; PBMC, peripheral blood mononuclear cell; SFC, spot-forming cells.

*CBC/Chemistries Performed at Charles Rivers and histopathology formally reviewed by a veterinary pathologist (GEMpath Inc.).

†Systemic delivery of AAVrh74.MHCK7.micro-dystrophin did not induce any anatomic lesions.

Conclusions

Construct optimized for use in DMD

- AAVrh74 efficiently transduces all muscle types
- Low pre-existing immunity for AAVrh74
- MHCK7 promoter allows for cardiac and skeletal transgene muscle expression

Preliminary preclinical results

- Widespread micro-dystrophin expression across all muscle types
- Reduction in CK
- Improved functional measures
- No toxicity

Evidence From Spinal Muscular Atrophy

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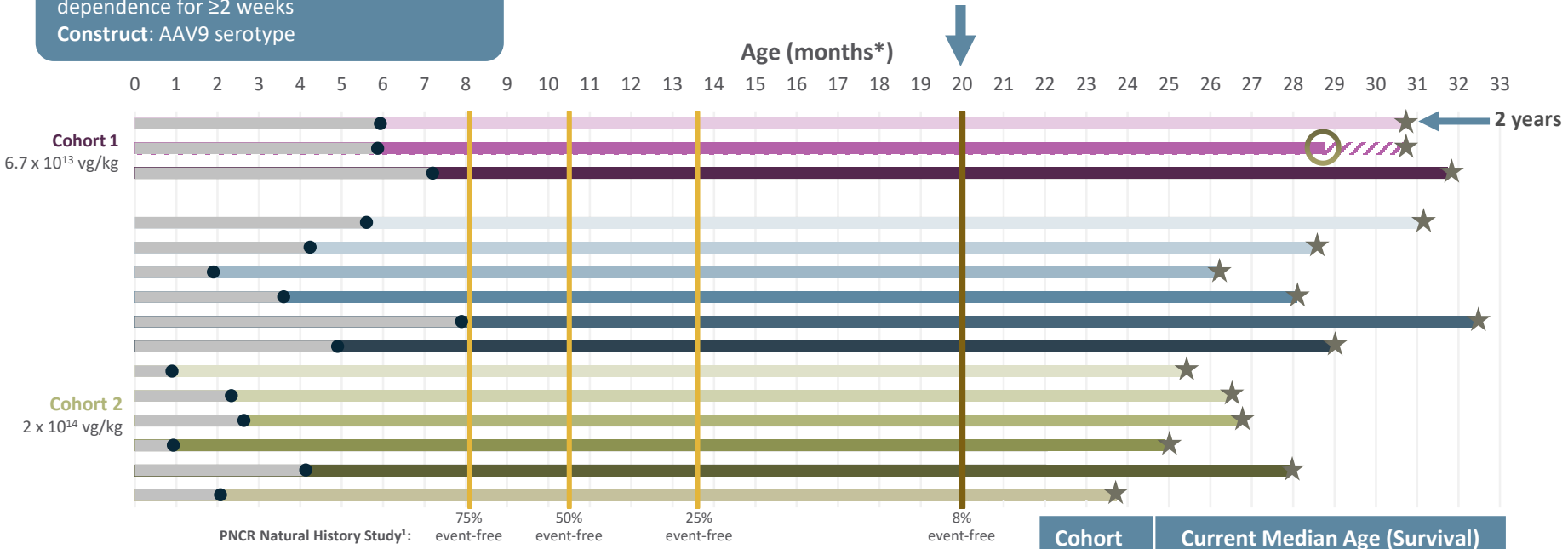
AVXS-101: Survival Data (as of Feb 2018)

Outcome: death or >16 hr/day of ventilator dependence for ≥2 weeks
Construct: AAV9 serotype



Cohort	Current Median Age (Survival) (months*)
1	47
2	33

PNCR, Pediatric Neuromuscular Clinical Research Network.
*Month defined as 30 days.
1. Finkel RS, et al. *Neurology*. 2014;83(9):810-817.

AVXS-101: Motor Milestones

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Two children are able to crawl, pull to a stand, and stand and walk independently

Cohort 2 2 x 10^{14} vg/kg	Age at gene therapy (months)	Motor Milestone Achievement							
							Sitting Unassisted		
		Brings hand to mouth	Head control	Partial roll*	Roll†	Sitting with assistance	≥5 seconds‡	≥10 seconds§	≥30 seconds‖
E.04	6	✓	✓	✓	✓	✓	✓		
E.05	4	✓	✓	✓	✓	✓	✓	✓	✓
E.06	2	✓	✓	✓	✓	✓	✓	✓	✓
E.07	4	✓	✓	✓	✓	✓	✓	✓	
E.08	8	✓							
E.09	5	✓	✓	✓	✓	✓	✓	✓	✓
E.10	1	✓	✓	✓	✓	✓	✓	✓	✓
E.11	2	✓	✓	✓	✓	✓	✓	✓	✓
E.12	3	✓	✓	✓	✓	✓	✓	✓	✓
E.13	1	✓	✓	✓	✓	✓	✓	✓	✓
E.14	4	✓	✓	✓	✓	✓	✓	✓	✓
E.15	2	✓	✓	✓	✓	✓	✓	✓	✓

*Bayley Scales of Infant and Toddler Development, item #20, rolls a minimum 180° from back in only one direction. †Bayley Scales of Infant and Toddler Development, item #20, rolls a minimum 180° from back to both left and right. ‡Sitting unassisted for ≥5 seconds is in accordance with the criteria of item 22 in the Bayley Scales of Infant and Toddler Development – gross motor subtest and surpasses the 3-second count used as a basis for sitting (test item 1) in the Hammersmith Functional Motor Scale – Expanded for SMA (HFMSE). §Sitting unassisted for ≥10 seconds is in accordance with the criteria in the World Health Organization – MultiCentre Growth Reference Study. ‖Sitting unassisted for ≥30 seconds defines functional independent sitting and is in accordance with the criteria of item 26 in the Bayley Scales of Infant and Toddler Development – gross motor subtest.

Gene Transfer at 4 Weeks (patient video)

Phase 1/2 Clinical Trial

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Open-label Trial Design

- 12 subjects with DMD – open trial
  - Cohort A: 6 subjects; 3 months-3 years of age
  - Cohort B: 6 subjects; 4-7 years of age
- Inclusion criteria
  - Confirmed *DMD* mutation between exons 18-58, inclusive
  - Negative for AAVrh74 antibodies

Cohort B (4-7 years of age) Endpoints

- **Primary endpoint**:
  - Safety
- **Secondary endpoints**:
  - Change in micro-dystrophin expression pre- vs post-treatment
  - Decrease in CK
  - 100-meter timed test (100m)
  - North Star Ambulatory Assessment (NSAA; 10-meter timed test included)
  - Timed Up and Go (TUG)
  - Ascend and descend 4 steps
  - Hand-held Dynamometry (HHD)
  - Cardiac MRI (at 1 year)

MRI, magnetic resonance imaging.

Clinical Study Results From Cohort B

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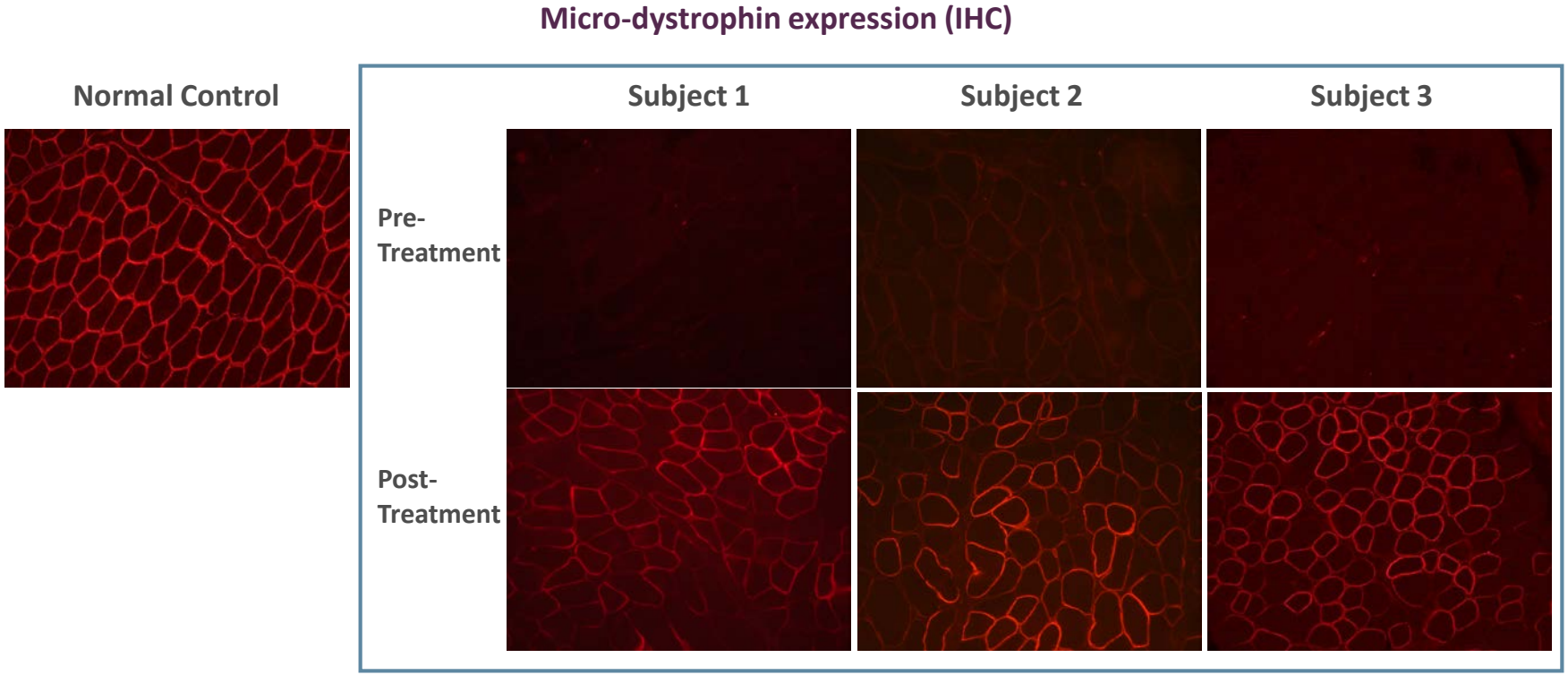
Subject Demographics at Baseline

Subject	Age (years)	CK Levels at Baseline (U/L)
1	5	20,691
2	4	23,414
3	6	34,942
4	4	29,210

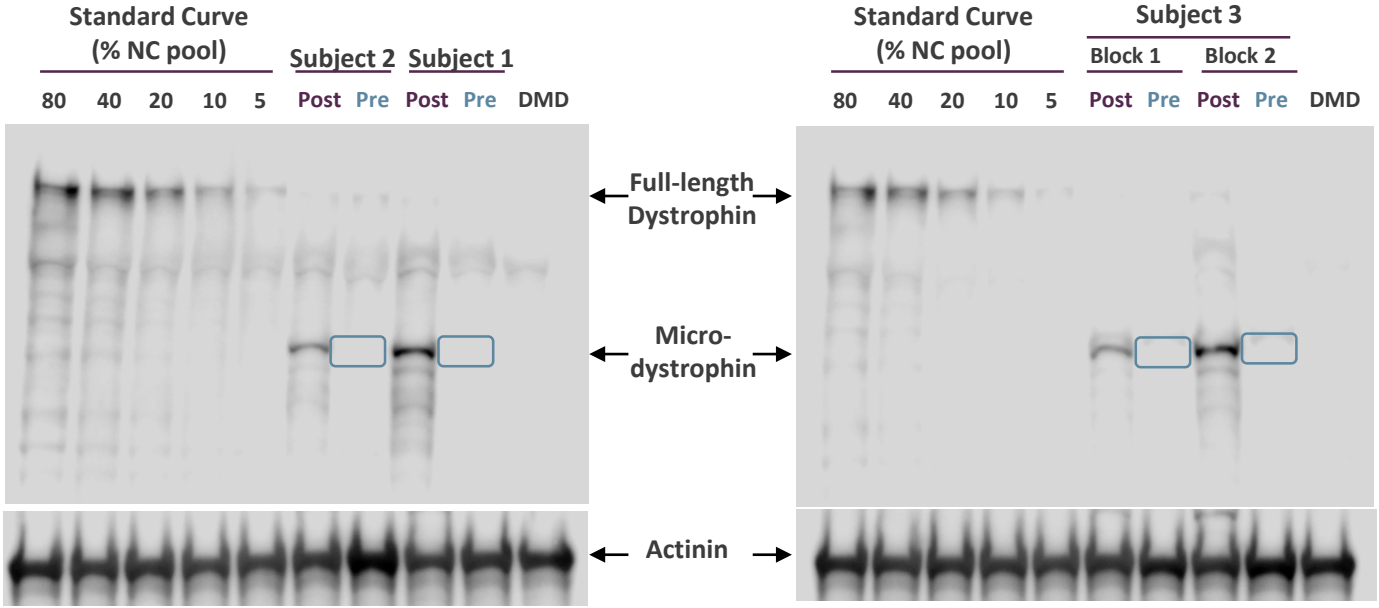
Robust Micro-dystrophin Expression in Muscle Fibers from the Gastrocnemius



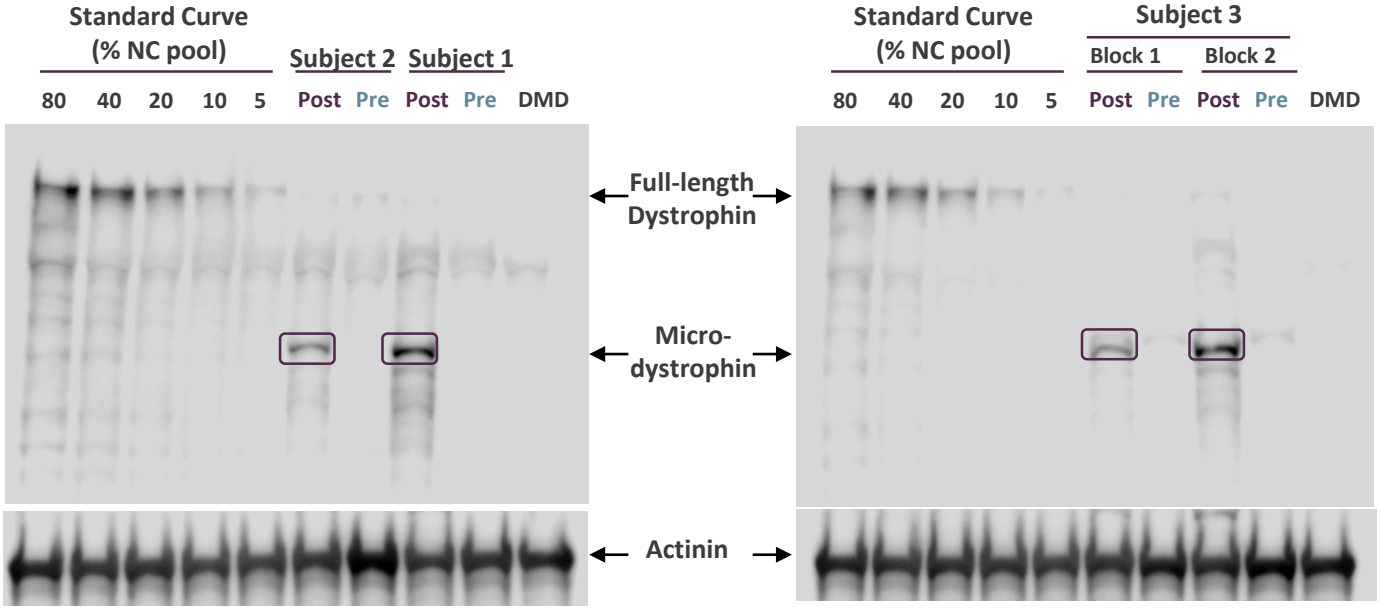
Robust Micro-dystrophin Expression in Muscle Fibers from the Gastrocnemius

Subject	Mean Intensity	Percentage of Dystrophin-Positive Fibers
1	82.0 %	78.0 %
2	59.0 %	73.5 %
3	83.0 %	77.0 %
Mean	**74.5 %**	**76.2 %**

Detection of Micro-dystrophin Expression by Western Blot Post-Treatment



Detection of Micro-dystrophin Expression by Western Blot Post-Treatment



Western quantitation method	Mean micro-dystrophin expression compared vs normal
Sarepta	**38.2%** (not adjusted for fat and fibrotic tissue)
Nationwide	**53.7%** (adjusted for fat and fibrotic tissue)

Vector Genome Copy Number Is >1 Copy Per Nucleus, Consistent With Micro-dystrophin Expression Levels

Subject	Vector Copies/µg DNA	Copies per Nucleus*
1	$>10^5$	1.7
2	$>10^5$	1.3
3	$>10^5$	1.9

*1 vector copy per nuclei translates to ~50% micro-dystrophin positive fibers

Creatine Kinase (CK) in DMD

- Increased permeability of the sarcolemma leads to the leakage of CK from muscle fibers
- Increased serum CK values are the hallmark of muscle damage, and are elevated in DMD (and other muscle diseases)
  - Markedly elevated CK values are diagnostic of DMD
- Peak serum CK values are usually observed in patients with DMD who are between the ages of 2 to 5 years[1]

1. Zatz M, et al. *J Neurol Sci* .1991;102:190–196.

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- After the age of 7 years, serum CK values decrease with time and clinical progression
  - Serum CK values decline at a rate of ~8% per year in patients who are >7 years of age

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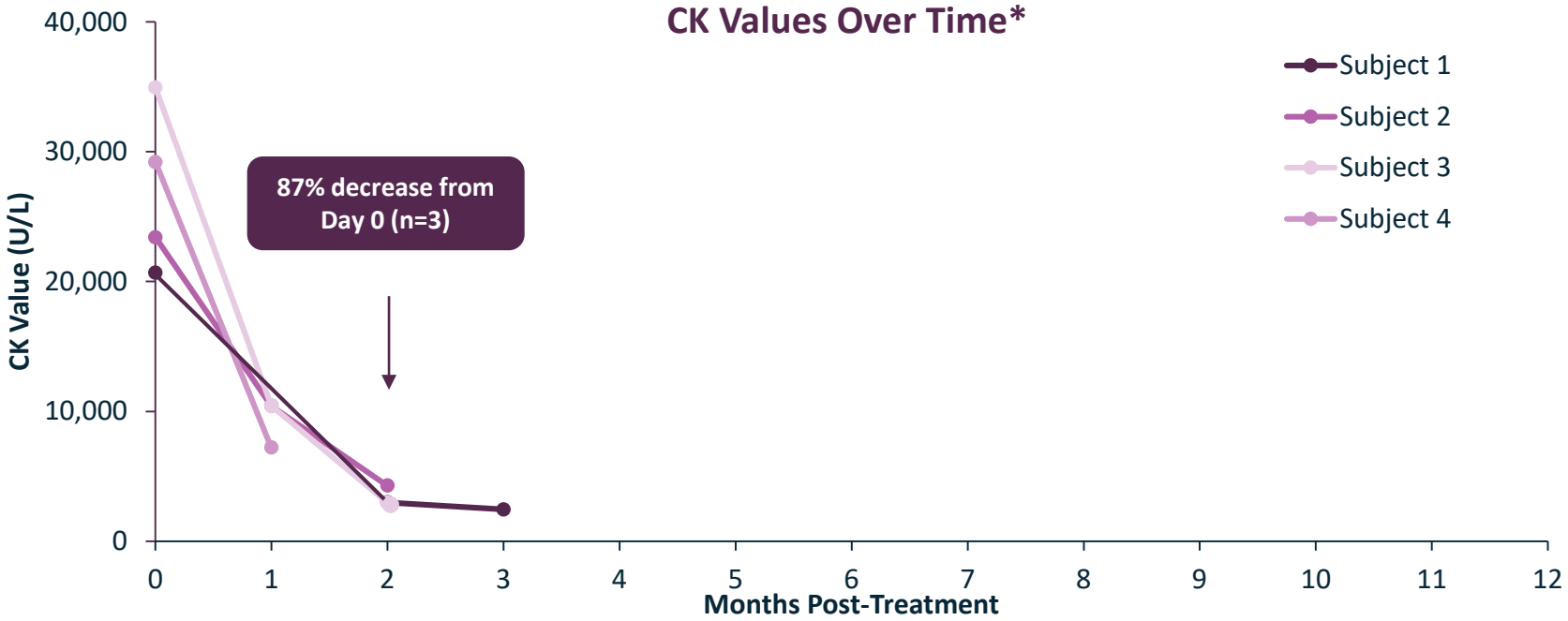
- After the age of 7 years, serum CK values decrease with time and clinical progression
  - Serum CK values decline at a rate of ~8% per year in patients who are >7 years of age
- The rate of serum CK values decrease is impacted by the extent of disease progression
  - The serum CK values of wheelchair-dependent patients, and patients with advanced muscle loss, decrease more slowly than other DMD patients

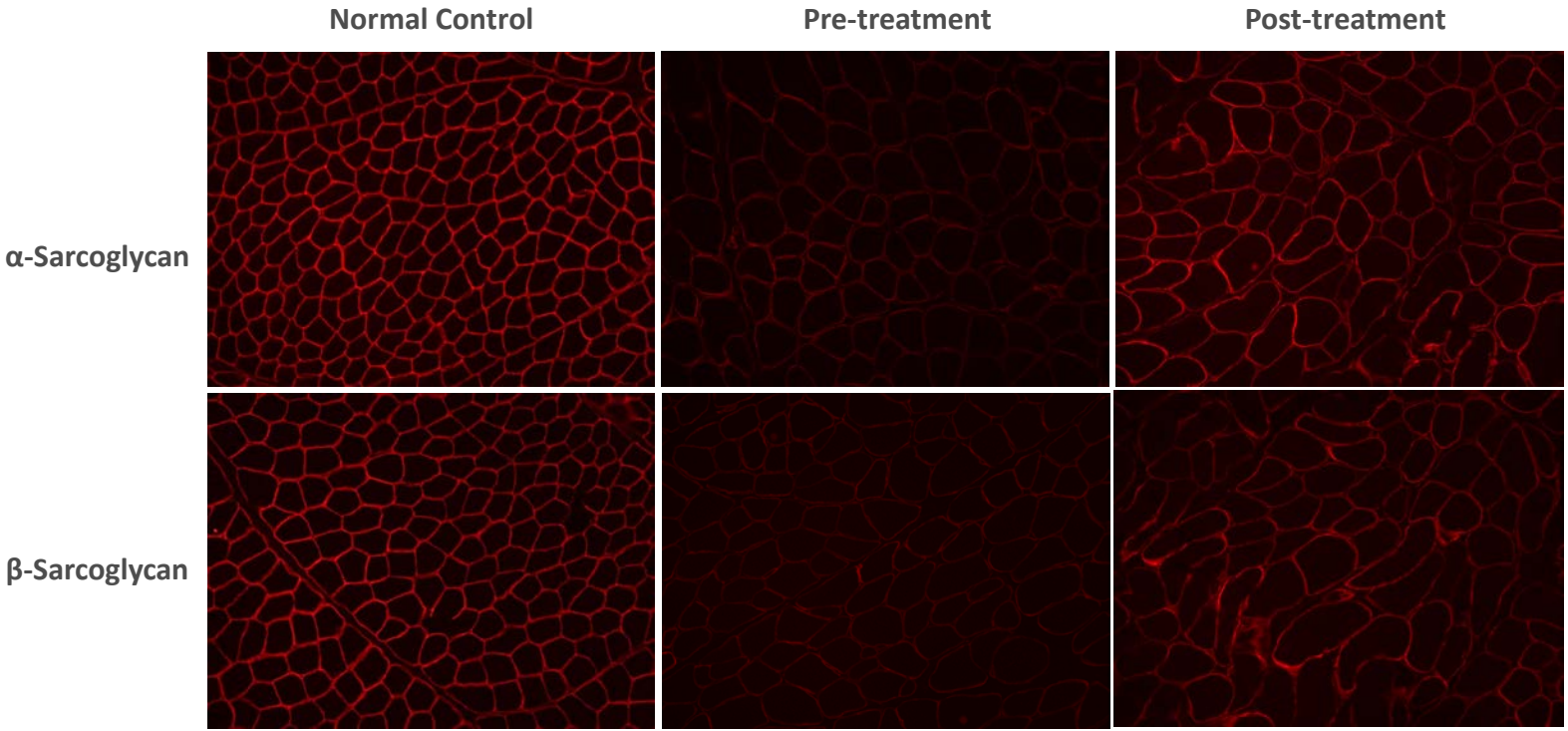
1. Zatz M, et al. *J Neurol Sci* .1991;102:190–196.

CK Levels Are Dramatically Reduced with Micro-dystrophin Therapy



Micro-dystrophin Gene Therapy Upregulates DAPC Proteins

Expression of DAPC Proteins in Muscle Fibers from the Gastrocnemius of Subject 2 (IHC)



Patient Videos

SAREPTA THERAPEUTICS

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

Patient Home Video: Stair Climbing

2 days post-treatment

60 days post-treatment

Patient Video

Post-treatment

Patient Home Video:
90 Days Post-Treatment

Safety

SAREPTA THERAPEUTICS

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

Safety (n=4)

- No Serious Adverse Events (SAEs) in this study
- 2 subjects had elevated GGT that resolved with increased steroids within a week and returned to baseline levels
- No other clinically significant laboratory findings
- Patients had transient nausea generally within the first week coincident with increased steroid dosing
  - Did not correlate with liver enzyme elevations or any other abnormality

GGT, gamma-glutamyl transpeptidase.

Adaptive Clinical Study Design

SAREPTA THERAPEUTICS

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

Cohort C (4-7 years of age): Addition of Placebo-controlled Study Cohort

Subjects

- Treatment arm, n=12
- Placebo arm, n=12
  - Crossover at 1 year

Endpoints

- **Primary**:
  - Safety
  - Demonstration of micro-dystrophin protein expression
- **Secondary**:
  - Decrease in CK
  - Time to rise
  - Ascend 4 steps
  - NSAA
  - 10-meter timed test
  - 100-meter timed test

Summary

Preliminary Clinical Results

- Consistent with preclinical results
- Widespread micro-dystrophin expression
- Upregulation of the DAPC complex
- Reduction in CK is unprecedented
- Vector genome copy levels (>1 copy/nucleus) are consistent with robust micro-dystrophin protein expression
- Use of the MHCK7 promoter will significantly alter DMD disease course in the heart
- New placebo-controlled study design could serve as the basis for registration

OUR VISION FOR THE FUTURE OF

Precision Genetic Medicine

SAREPTA THERAPEUTICS 2018 R&D DAY

Genome Editing for Duchenne Muscular Dystrophy

Charles A. Gersbach, PhD

Associate Professor of Biomedical Engineering

Duke University

Durham, NC

SAREPTA THERAPEUTICS

Duke UNIVERSITY

Today's Presentation

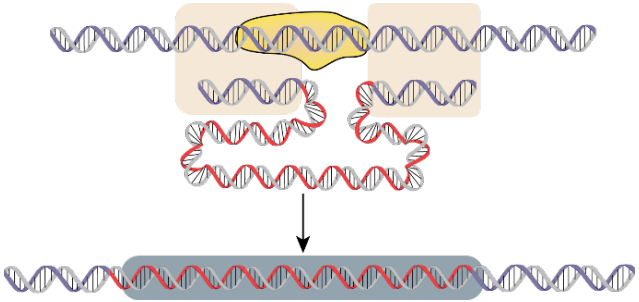
- Genome editing overview
- Genome editing for DMD
- CRISPR editing of dystrophin in DMD patient cells
- CRISPR editing of dystrophin in *mdx* mice
- Development of a humanized mouse model of DMD
- CRISPR editing of dystrophin in satellite muscle cells
- Summary and next steps

CRISPR, clustered regularly interspaced short palindromic repeats; DMD, Duchenne muscular dystrophy.

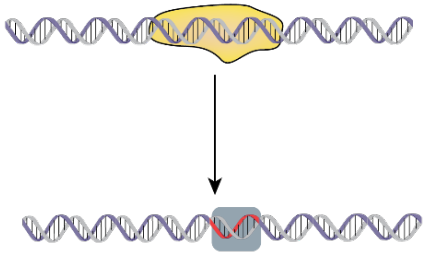
Genome Editing to Treat Genetic Disease

Genomics Research from Technology Networks. CRISPR: Emerging applications for genome editing technology. www.technologynetworks.com/genomics/articles/crispr-emerging-applications-for-genome-editing-technology-288978. Accessed June 6, 2018.

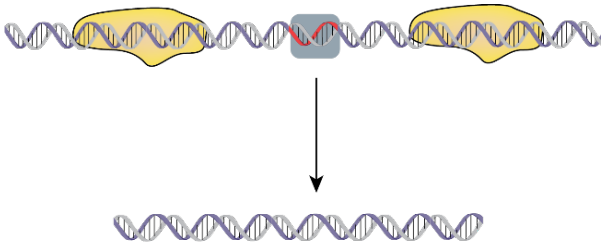
Genome Editing to Treat Genetic Disease



Inserting DNA:
HDR exon replacement
NHEJ targeted integration



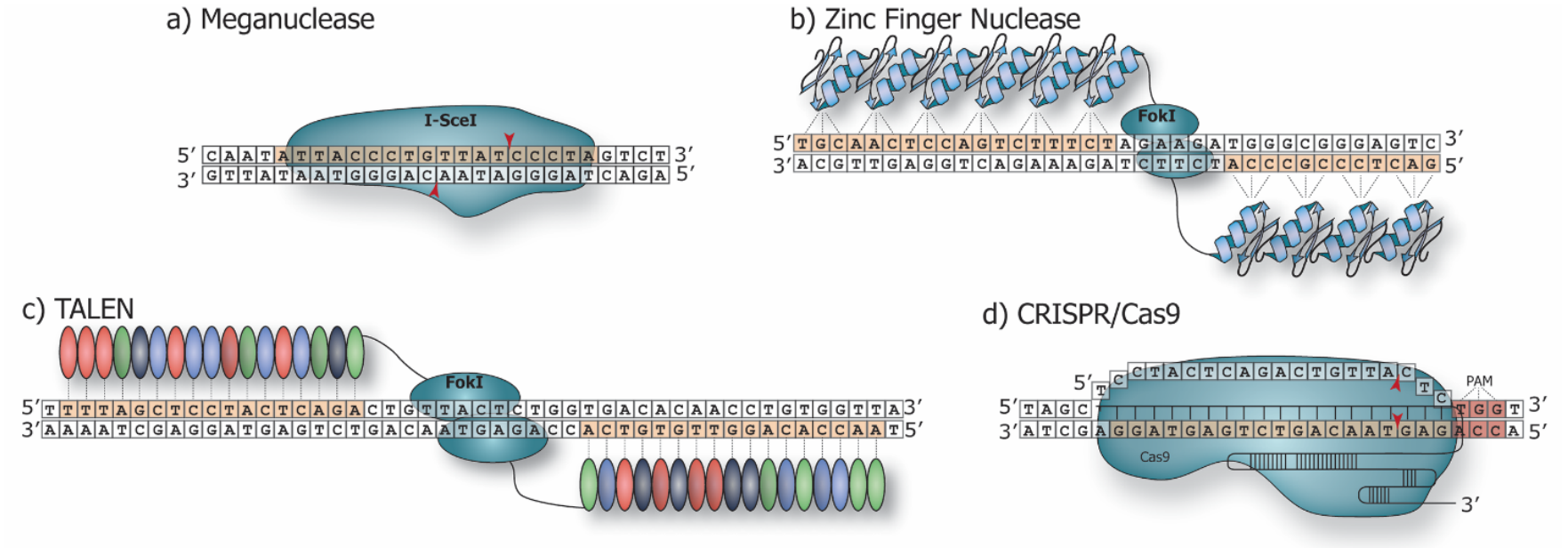
Shifting DNA:
NHEJ - frame shifting
Splice-site targeting



Excising DNA:
Exon deletion

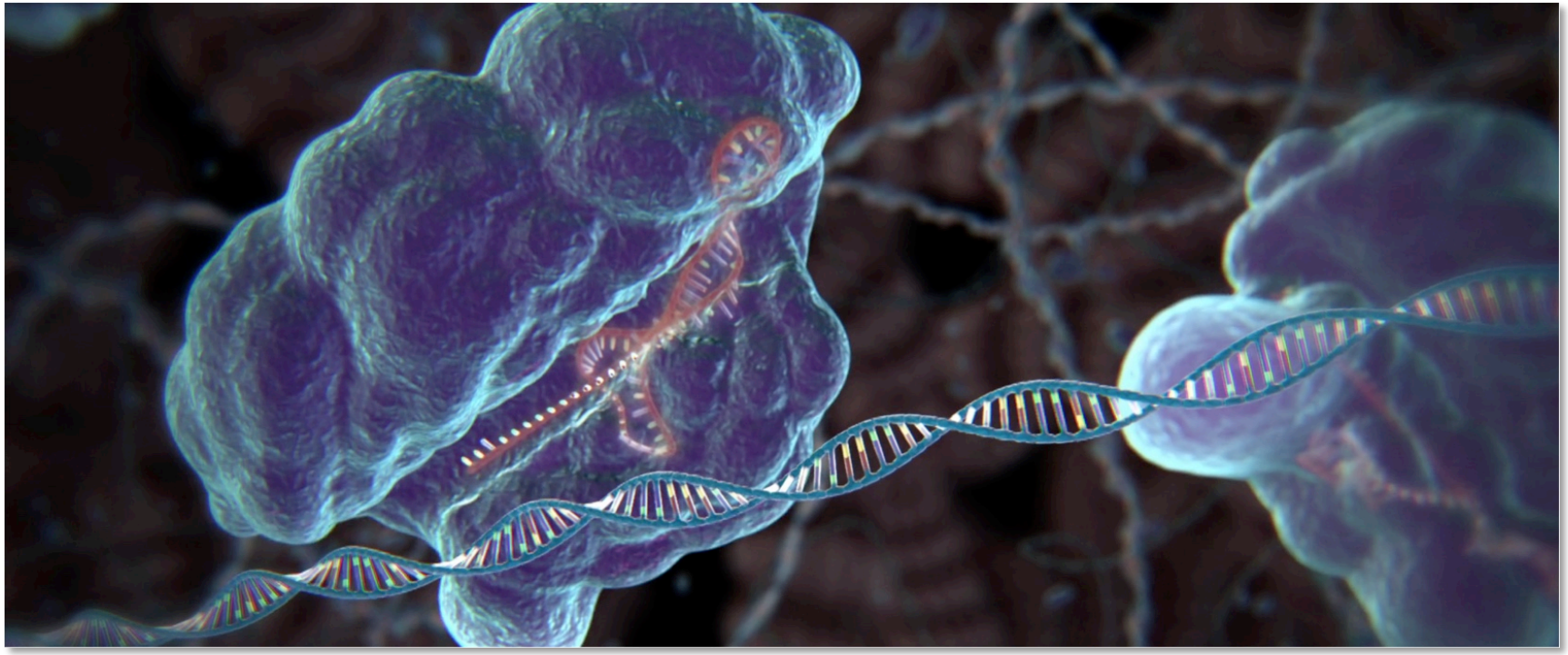
HDR, homology-directed repair; NHEJ, non-homologous end joining.
Nelson CE, Gersbach CA. *Annu Rev Chem Biomol Eng*. 2016;7:637-662.

Genome Editing Nucleases – Enzymes That Cut DNA



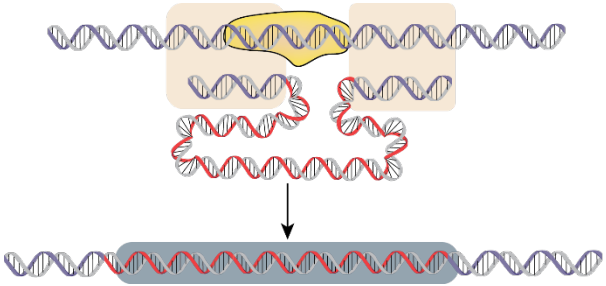
Cas9, CRISPR-associated protein 9; TALEN, transcription activator-like effector nuclease.
Nelson CE, Gersbach CA. *Annu Rev Chem Biomol Eng*. 2016;7:637-662.

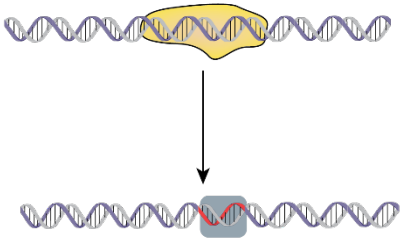
CRISPR-Cas9 Genome Editing

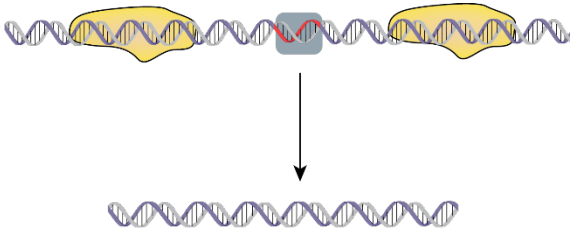


McGovern Institute for Brain Research at Massachusetts Institute of Technology.

Genome Editing to Treat DMD



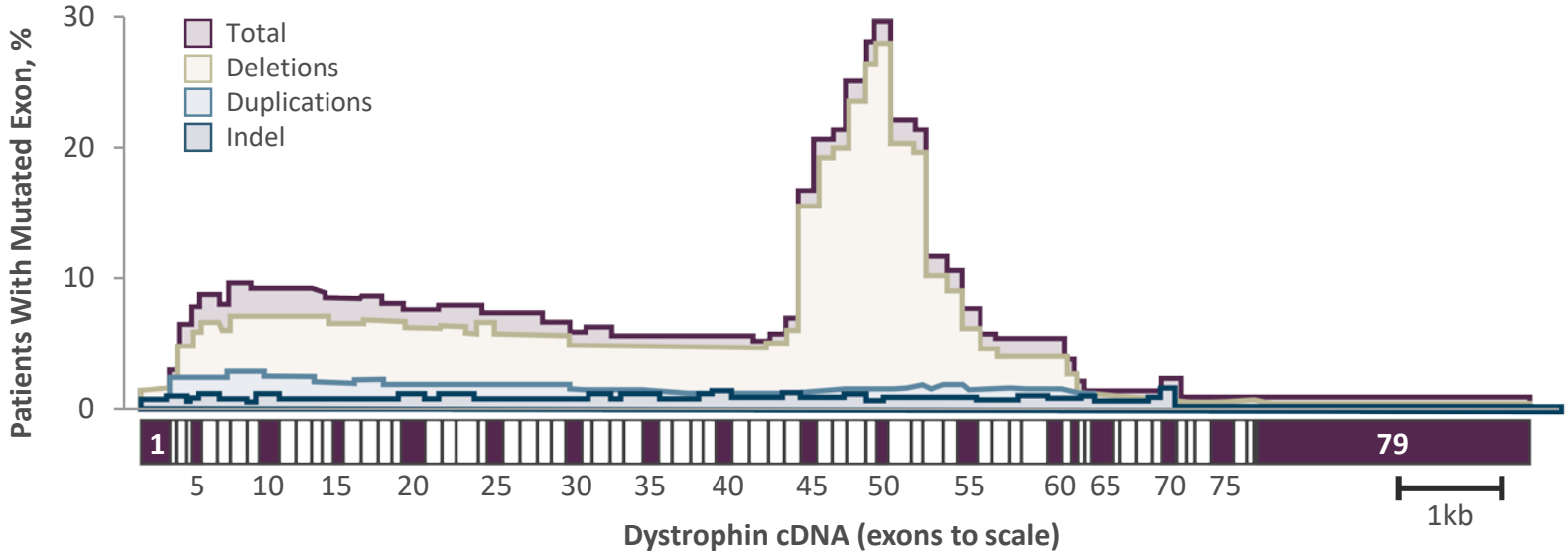




- Why genome editing for DMD?
  - Unmet clinical need
  - Viable delivery options
  - Multinucleated muscle fibers allow for many shots on goal within 1 cell
  - Potential to correct muscle stem cells
  - Many editing options to restore functional dystrophin

Nelson CE, Gersbach CA. *Annu Rev Chem Biomol Eng*. 2016;7:637-662.

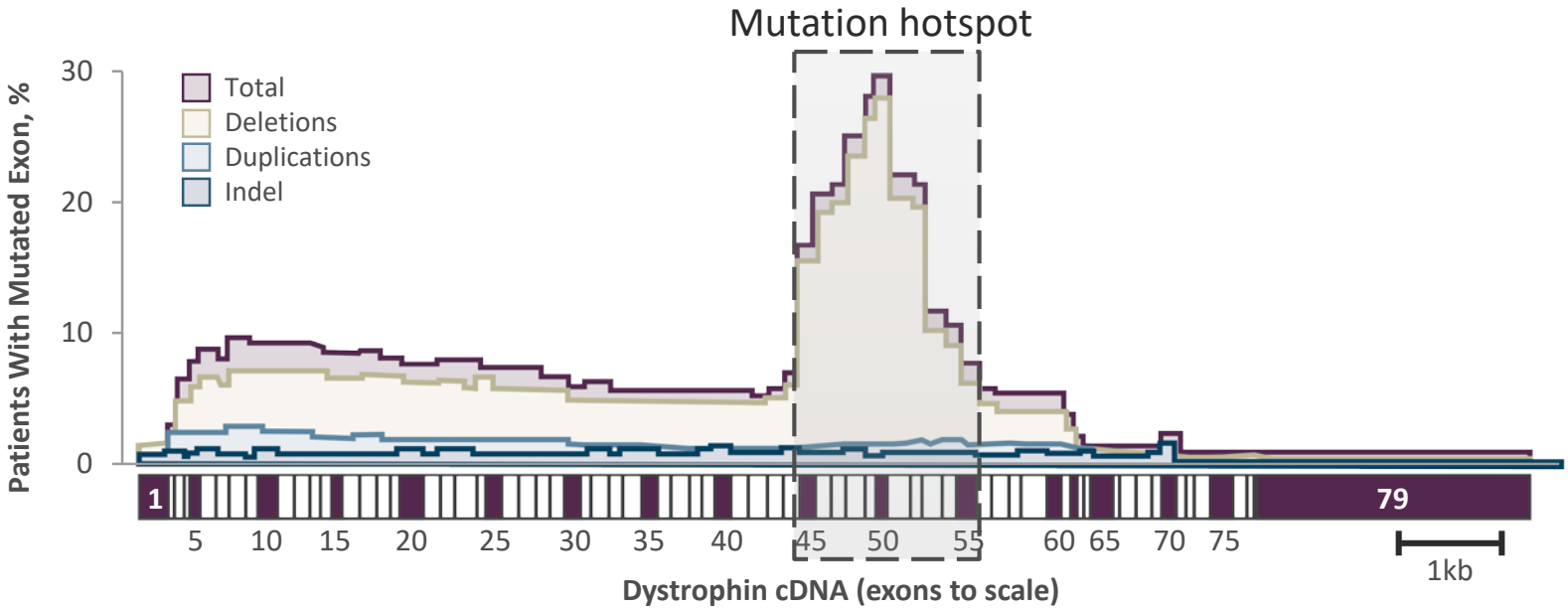
DMD Mutations[1,2]



- Excision of exons 45-55 with a single gene editing step could address 40%-63% of DMD patients[2]

1. Nelson CE and Gersbach CA. *Muscle Gene Therapy*. Data from the UMD database.
2. Fairclough RJ, et al. *Nat Rev Genet*. 2013;14(6):373-378.

DMD Mutations[1,2]



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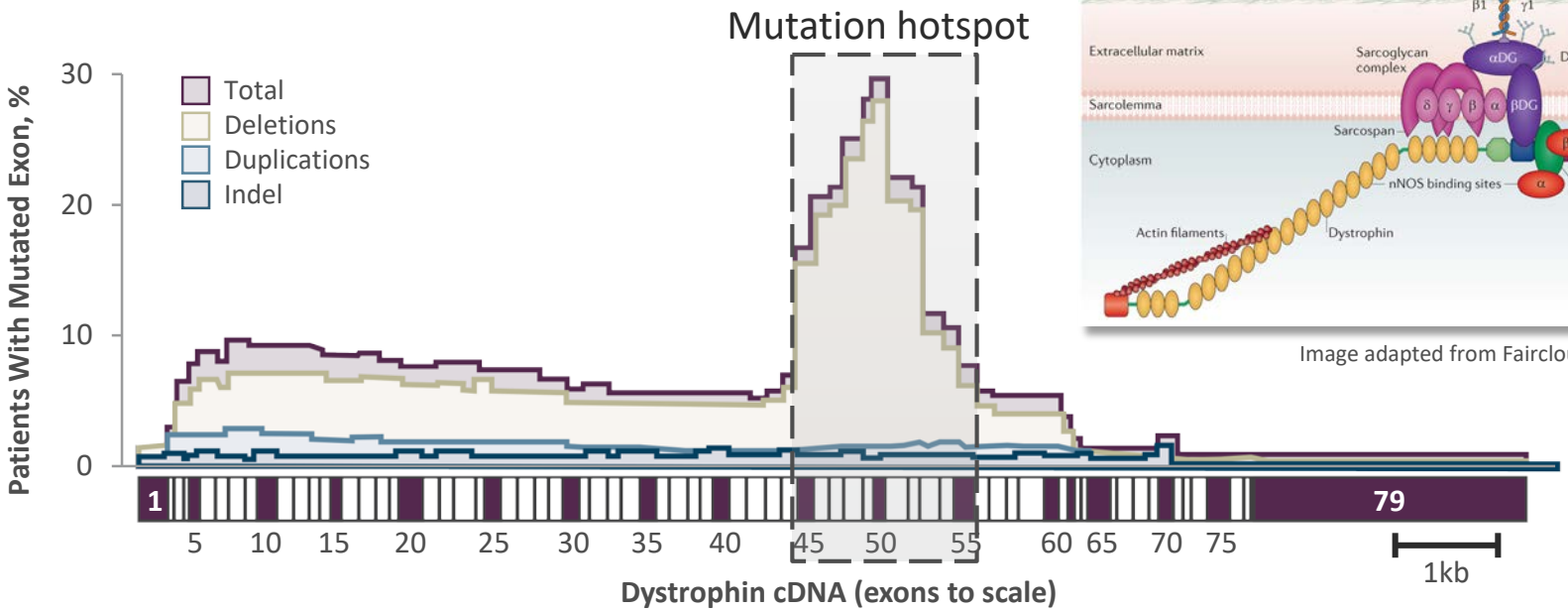

Image adapted from Fairclough RJ, et al.[2]

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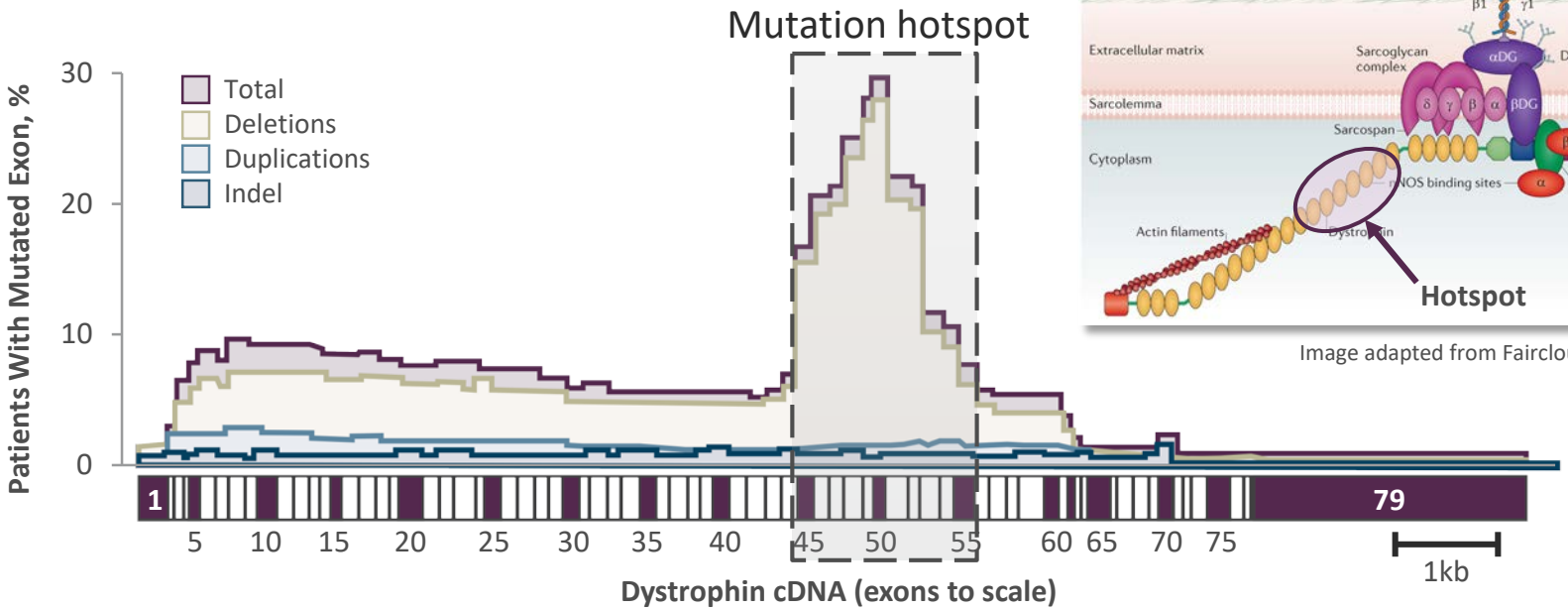

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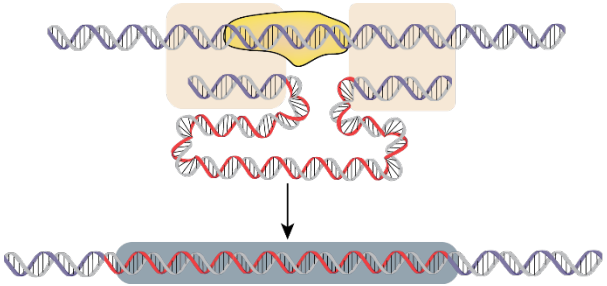
Genome Editing to Treat DMD[1]



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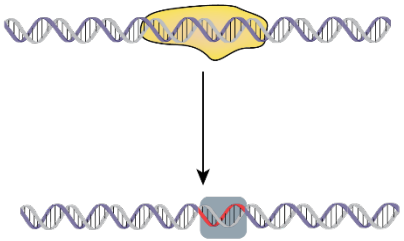

Shifting DNA:
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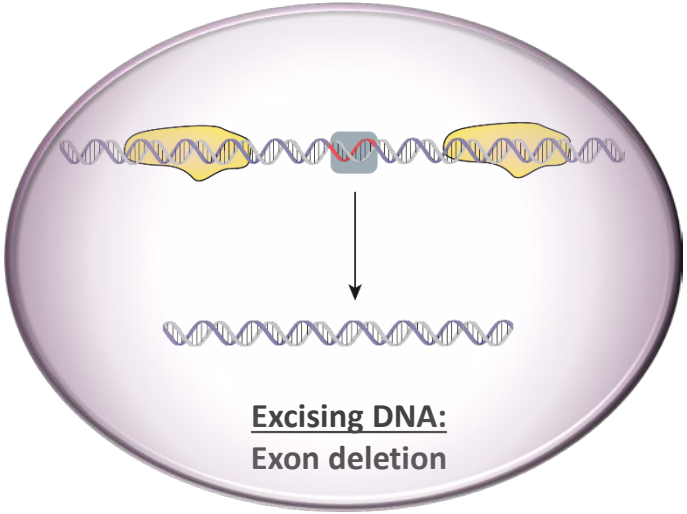


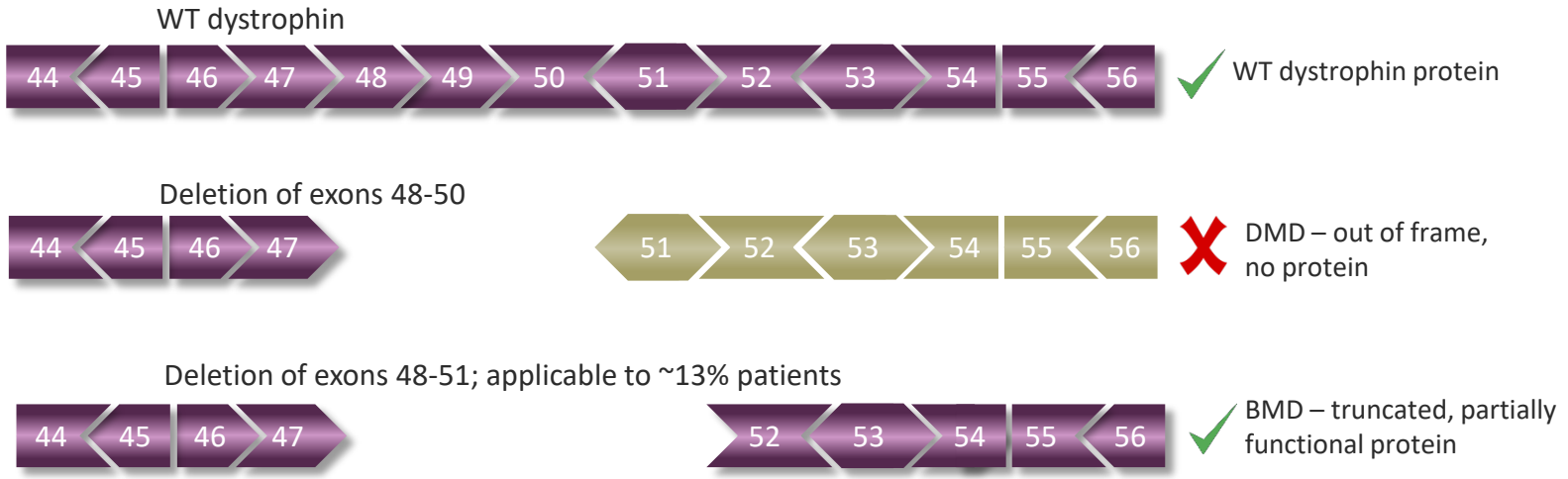
Excising DNA:
Exon deletion

- Why exon deletion?
  - Does not require HDR
  - Large introns provide flexibility in gRNA design and target choice
  - Single genome editing strategy can apply to 40%-63% of DMD patients[2]

gRNA, guide ribonucleic acid.

1. Nelson CE, Gersbach CA. *Annu Rev Chem Biomol Eng*. 2016;7:637-662.
2. Fairclough RJ, et al. *Nat Rev Genet*. 2013;14(6):373-378.

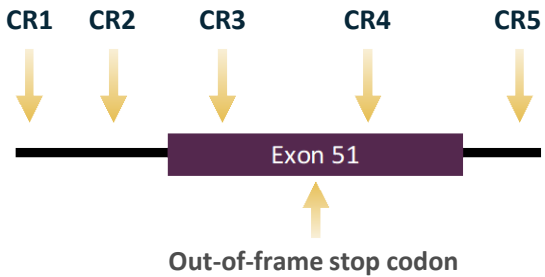
Genome Editing to Treat DMD



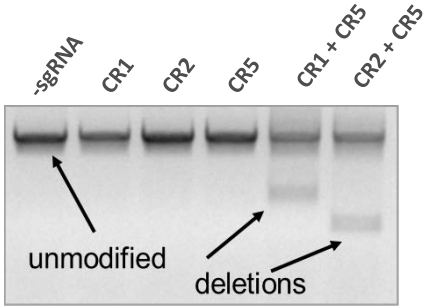
BMD, Becker muscular dystrophy; WT, wild-type.
Robinson-Hamm JN, Gersbach CA. *Hum Genet.* 2016;135(9):1029-1040.

CRISPR-based Genome Editing Restores Dystrophin in Patient Cells

gRNAs Used to Generate Deletions in Exon 51 Human DMD Myoblasts With a Deletion of Exons 48-50

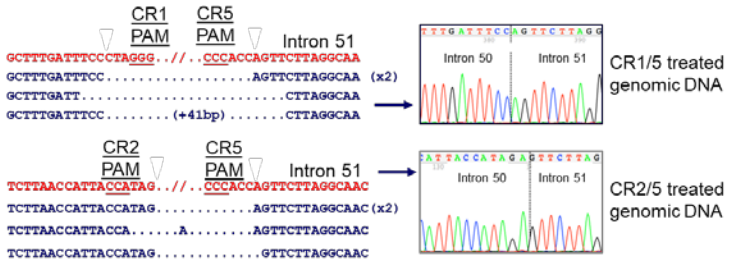


Endpoint Genomic PCR Across the Exon 51 Locus in Human DMD Myoblasts With a Deletion of Exons 48-50



Deleted: 13.6% 10.5%

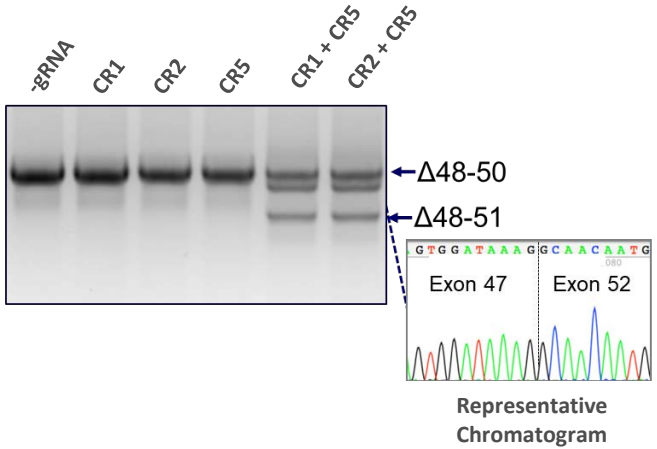
Sequencing of PCR Clones With Representative Chromatograms



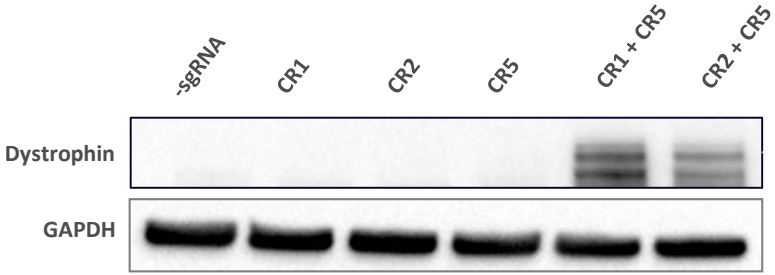
PAM, protospacer-adjacent motif; PCR, polymerase chain reaction; sgRNA, single guide RNA.
Ousterout DG, et al. *Nat Commun*. 2015;6:6244.

CRISPR-based Genome Editing Restores Dystrophin in Patient Cells

End-point RT-PCR Analysis of Dystrophin mRNA Transcripts in CRISPR/Cas9-modified Human Δ48-50 DMD Myoblasts

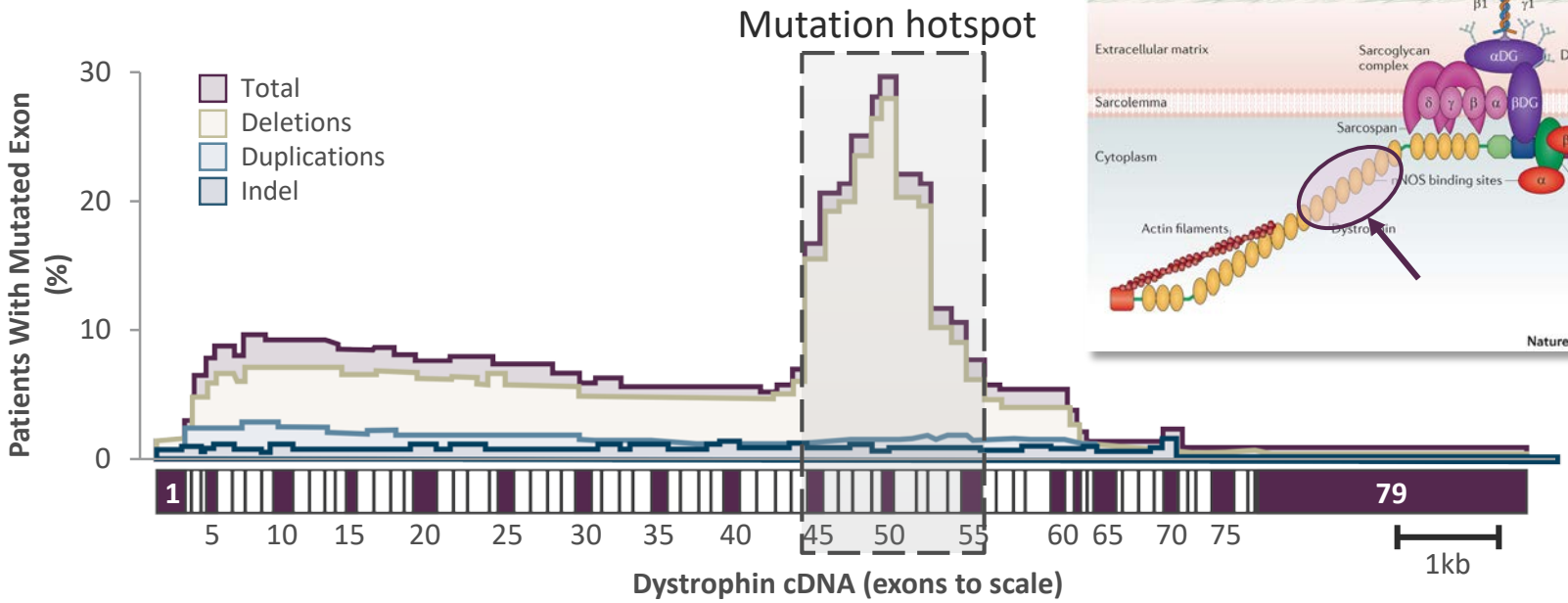


Analysis of Restored Dystrophin Protein Expression by Western Blot in CRISPR/Cas9-modified Human Δ48-50 DMD Myoblasts



GAPDH, glyceraldehyde-3-phosphate dehydrogenase; mRNA, messenger RNA; RT-PCR, reverse transcriptase polymerase chain reaction.
Ousterout DG, et al. *Nat Commun*. 2015;6:6244.

DMD Mutations[1,2]



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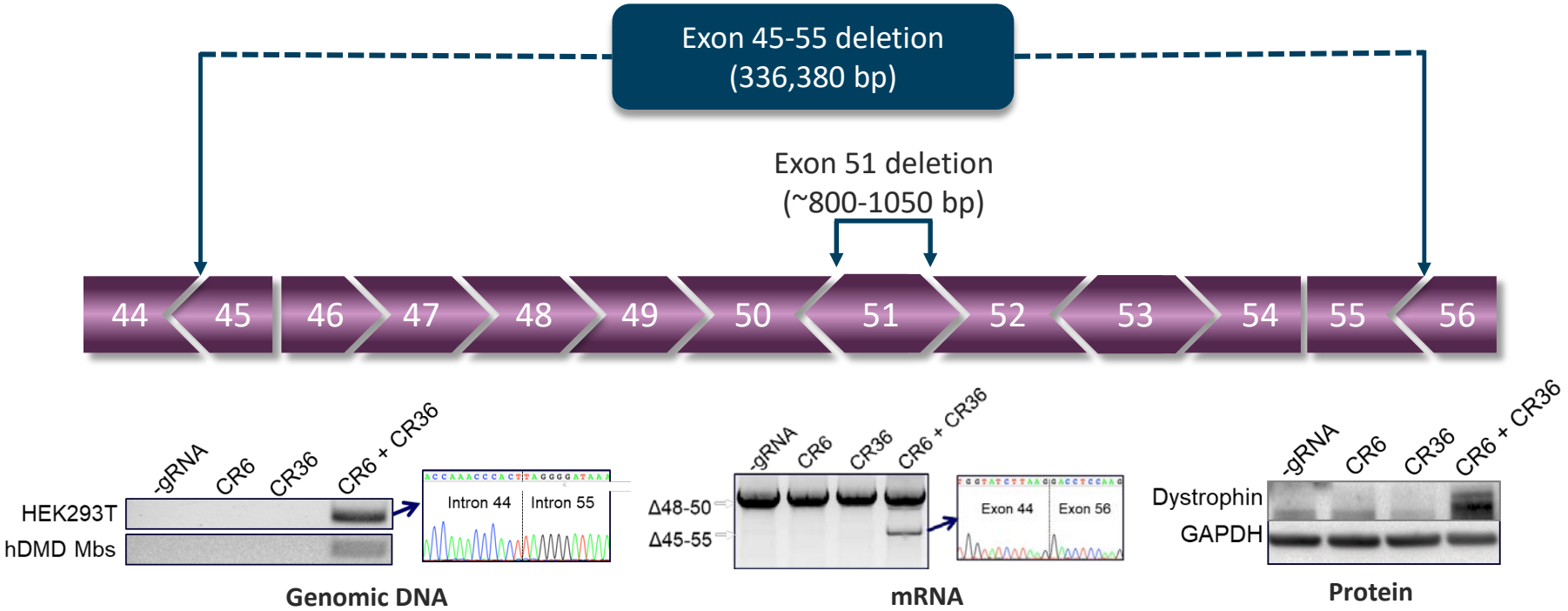
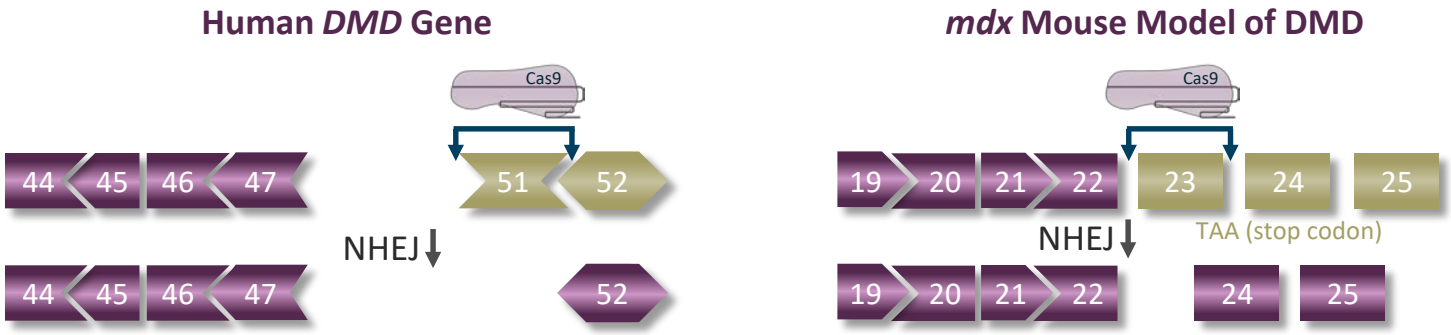
A Single Genome Editing Strategy for Half of All DMD Patients



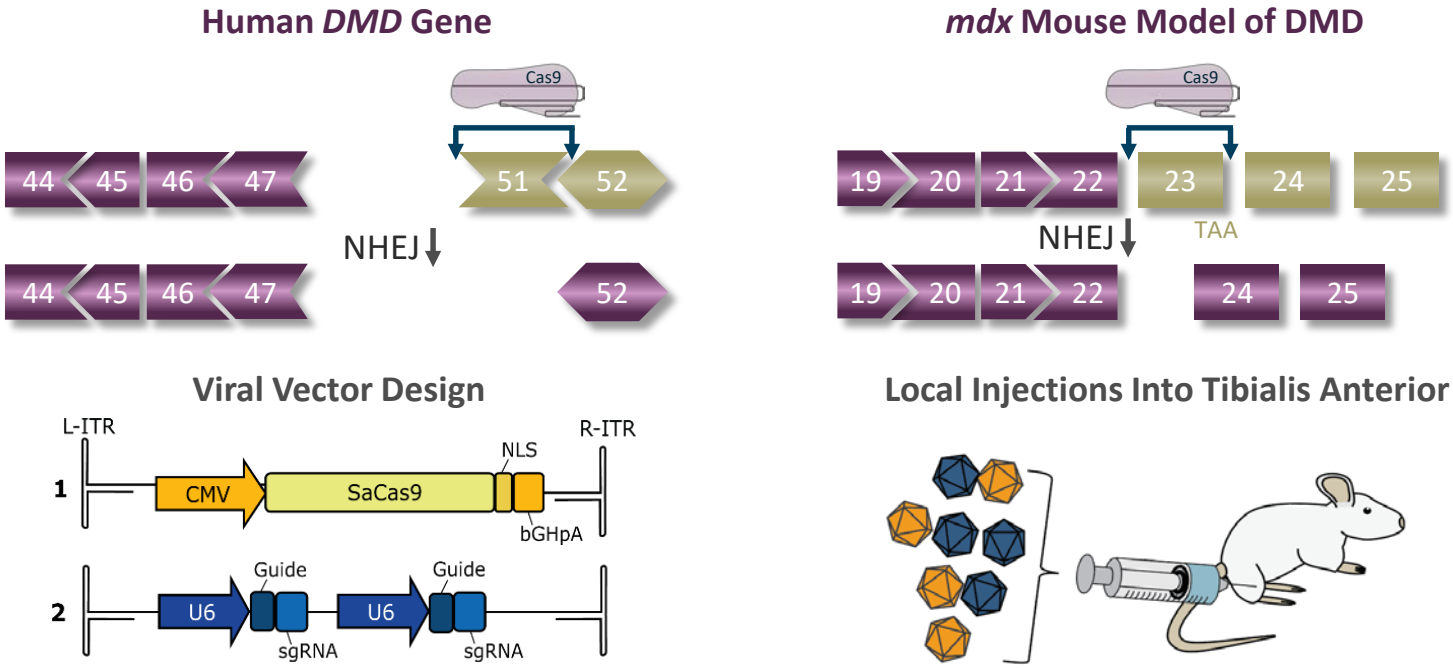
bp, base pairs; hDMD, human DMD, Mbs, myoblasts.
Ousterout DG, et al. *Nat Commun*. 2015;6:6244.

Genome Editing to Treat the *mdx* Mouse Model of DMD



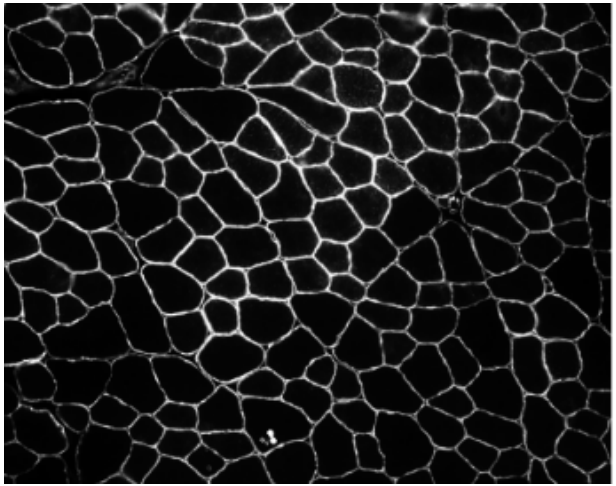
Nelson CE, et al. *Science.* 2016;351(6271):403-407.

Genome Editing to Treat the *mdx* Mouse Model of DMD



bGHpA, bovine growth hormone polyadenylation sequence; CMV, cytomegalovirus; ITR, inverted tandem repeat; NLS, nuclear localization signal; SaCas9, *Staphylococcus aureus* Cas9.
Nelson CE, et al. *Science.* 2016;351(6271):403-407.

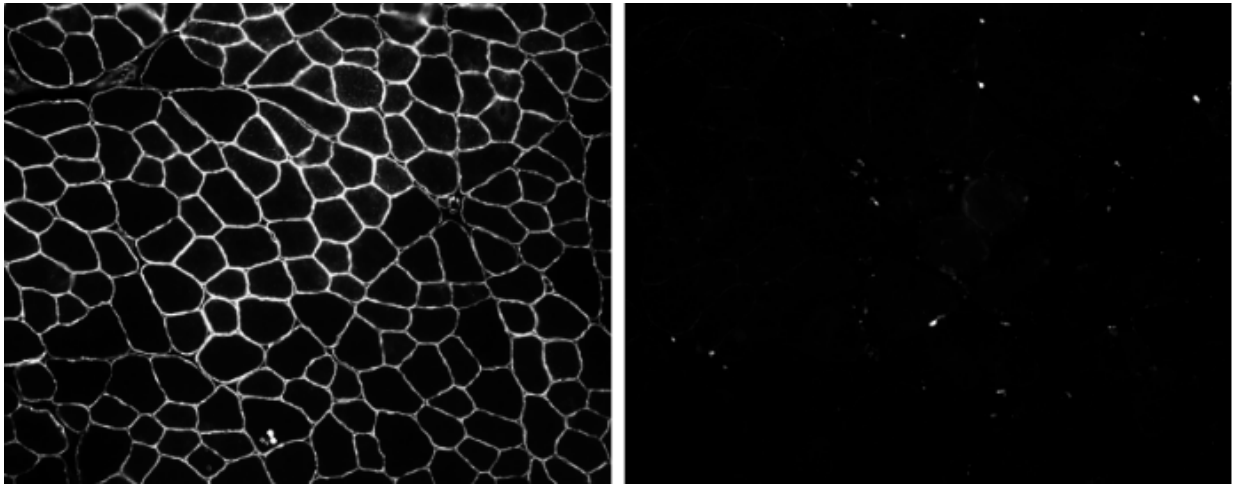
Genome Editing to Treat *mdx* Mouse Model of DMD



WT

Nelson CE, et al. *Science.* 2016;351(6271):403-407.

Genome Editing to Treat *mdx* Mouse Model of DMD



WT *mdx*

Nelson CE, et al. *Science.* 2016;351(6271):403-407.

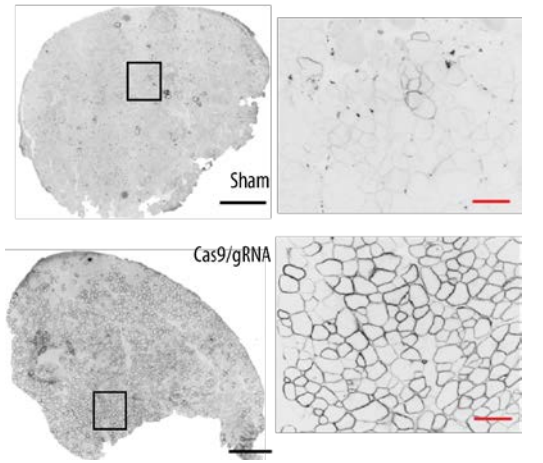
AAV-CRISPR Restores Dystrophin Expression in ~70% of Muscle Fibers

WT | *mdx* | *mdx* + AAV-CRISPR

AAV, adeno-associated virus.
Nelson CE, et al. *Science.* 2016;351(6271):403-407.

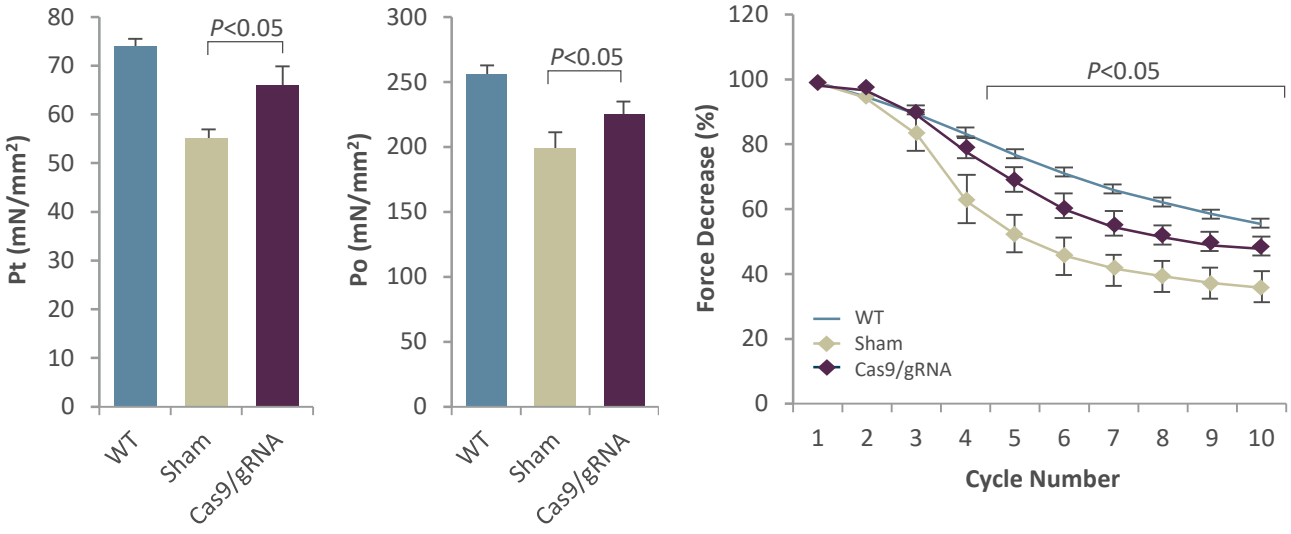
Dystrophin Expressed in ~70% of Muscle Fibers Resulting in Increased Muscle Force and Decreased Fatigue

Dystrophin Staining[1]



Whole Muscle Transverse Sections

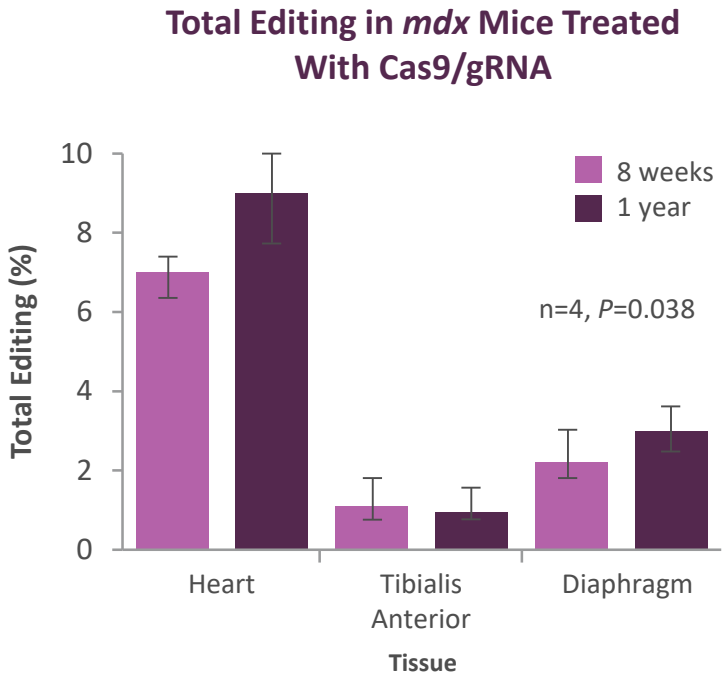
In situ Muscle Function Assay[1,2]



Po, tetanic force; Pt, specific twitch force.

1. Nelson CE, et al. *Science.* 2016;351(6271):403-407.
2. Hakim CH, et al. *J Vis Exp*. 2013;(72).

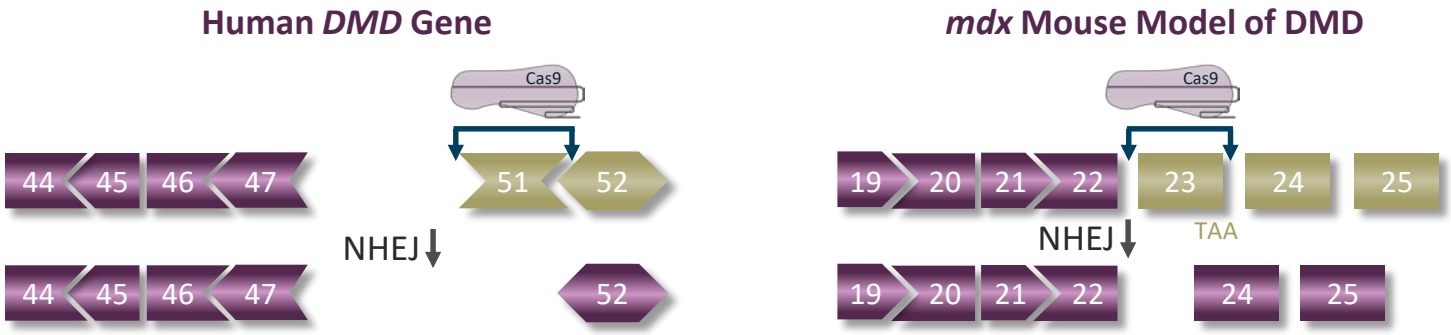
Significant Increase in Editing Frequency From 8 Weeks to 1 Year in the *mdx* Mouse Model of DMD



- Systemic delivery to neonatal mice
- No obvious toxicity or adverse events
- Minimal off-target activity

Nelson CE, et al. Presented at: 21st Annual Meeting of the American Society of Gene and Cell Therapy; May 16-19, 2018; Chicago, IL.

A Humanized Mouse Model of DMD for Preclinical Development



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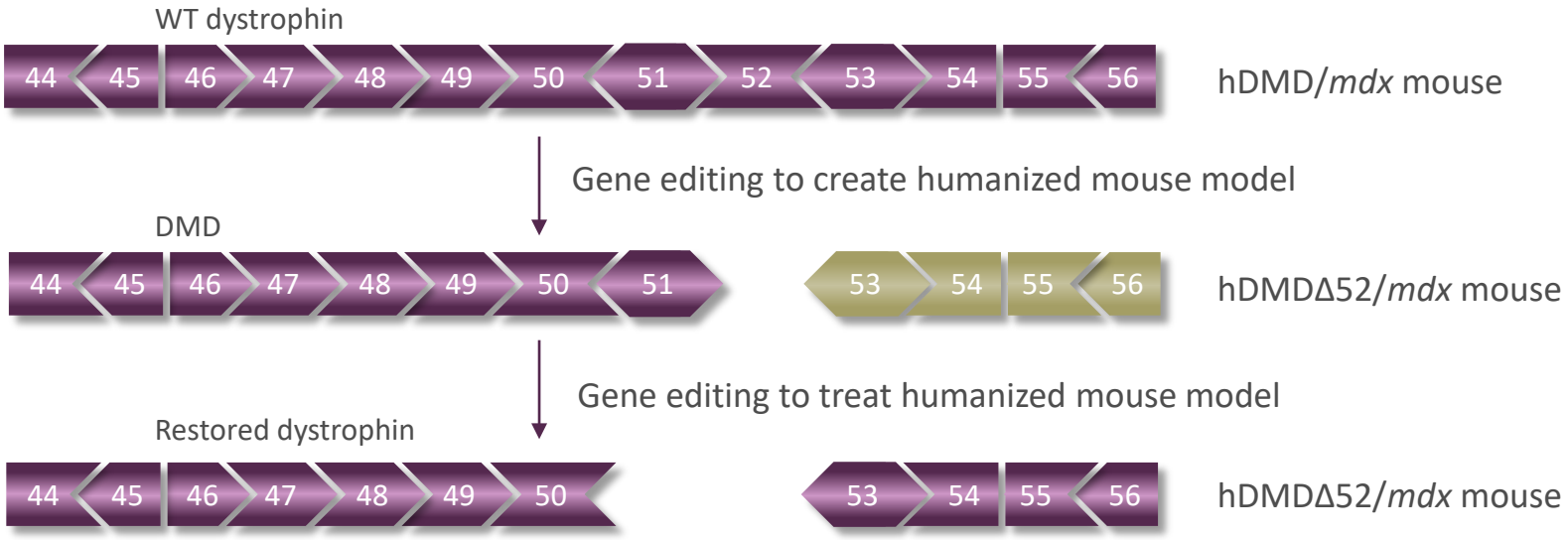
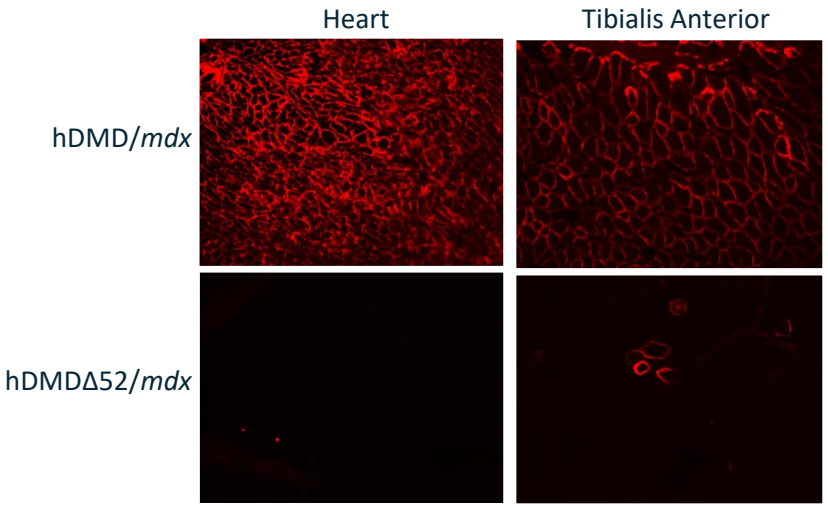


1. 't Hoen PA, et al. *J Biol Chem*. 2008;283(9):5899-5907.
2. Robinson-Hamm JN, et al. Presented at: 21st Annual Meeting of the American Society of Gene and Cell Therapy; May 16-19, 2018; Chicago, IL.

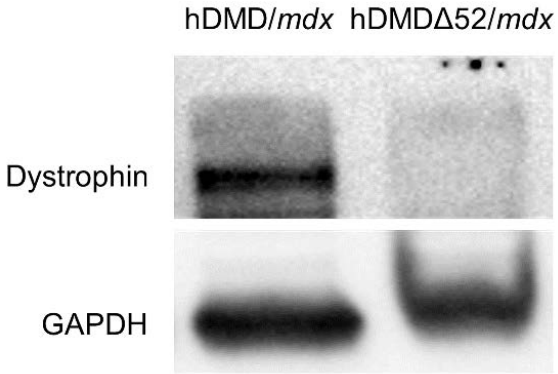
A Humanized Mouse Model of DMD for Preclinical Development

hDMDΔ52/*mdx* mouse

Immunohistochemistry



Immunoblot



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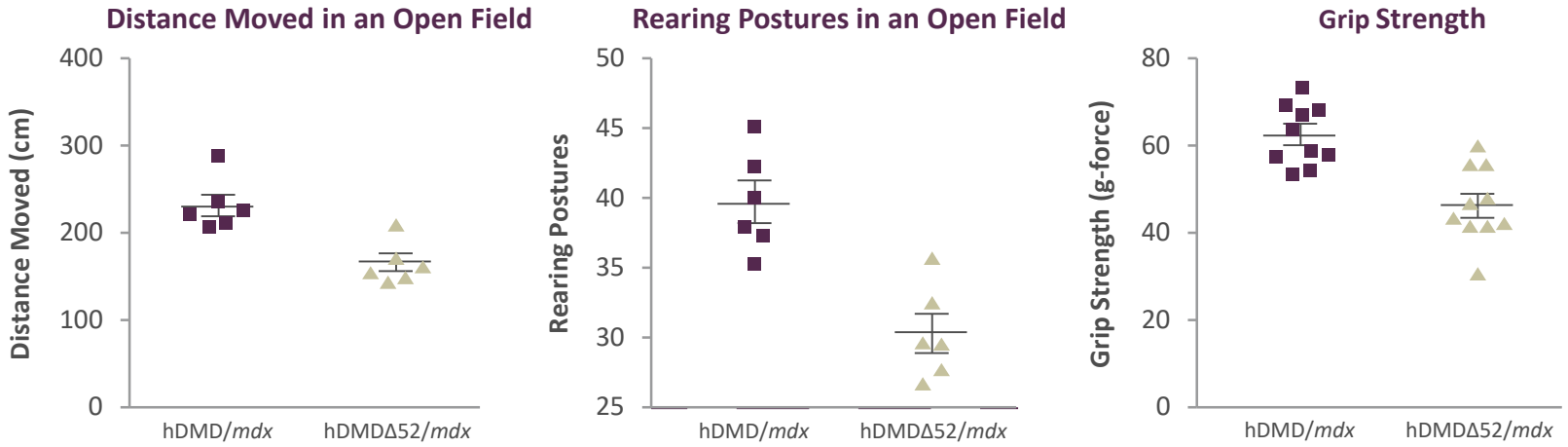
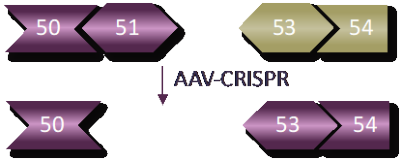
A Humanized Mouse Model of DMD for Preclinical Development

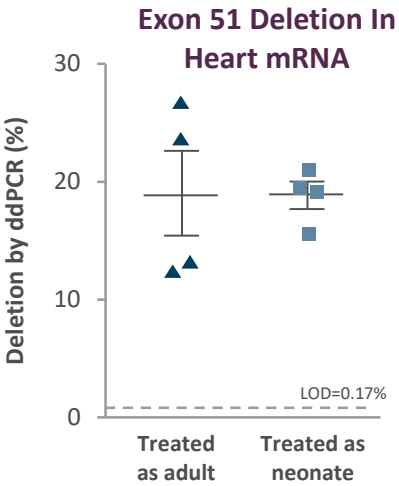
hDMDΔ52/*mdx* mouse

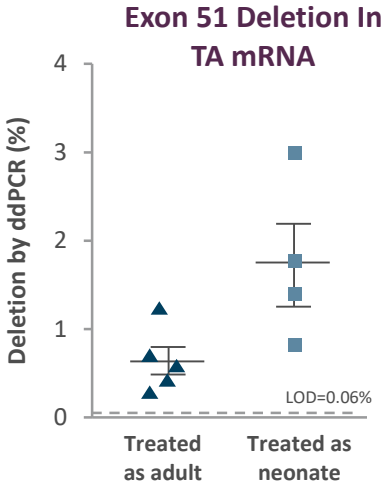


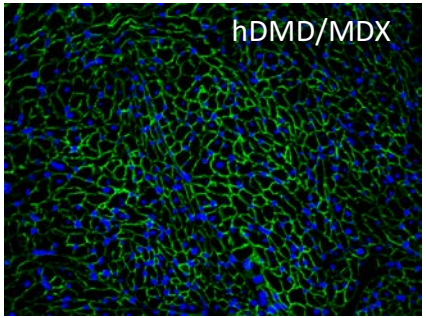
Robinson-Hamm JN, et al. Presented at: 21st Annual Meeting of the American Society of Gene and Cell Therapy; May 16-19, 2018; Chicago, IL.

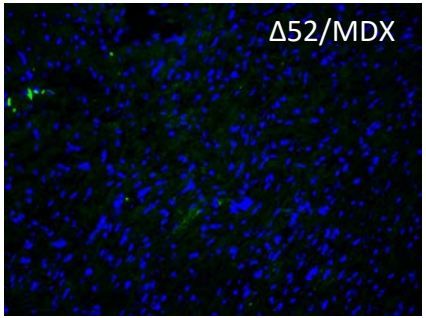
AAV-CRISPR Restores Human Dystrophin in Humanized DMD Model

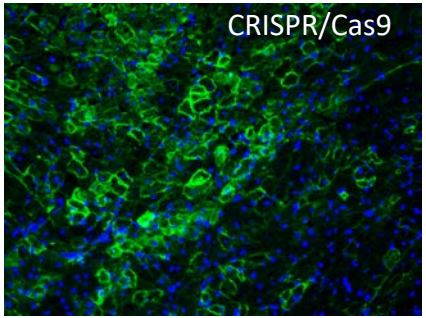










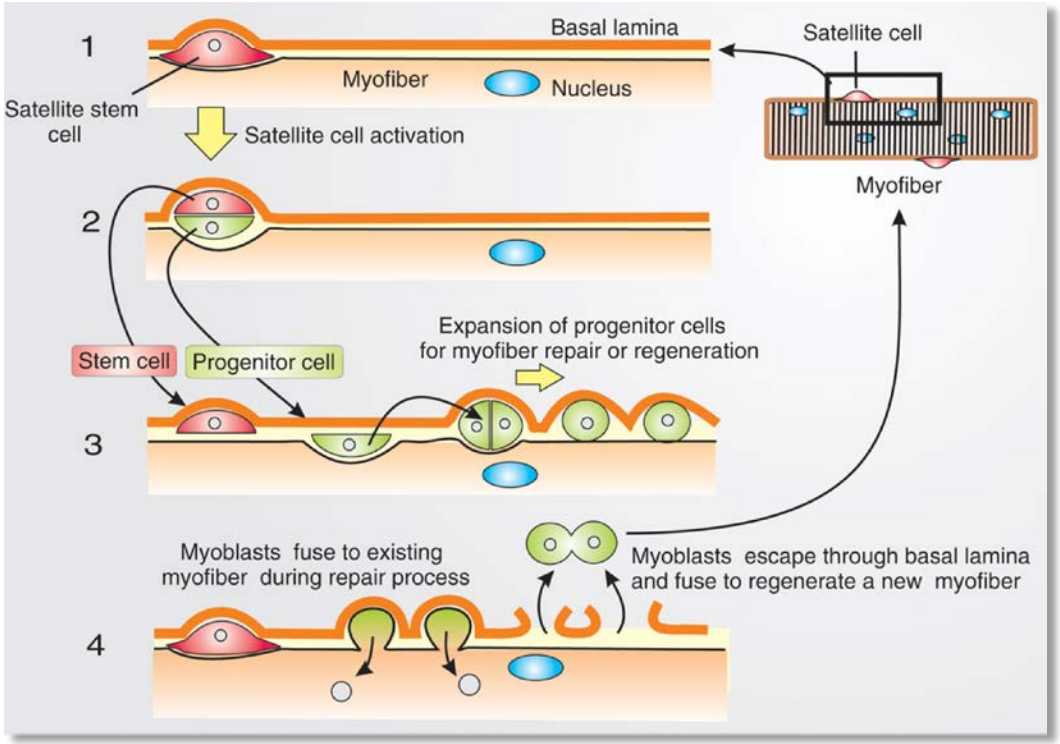


DYSTROPHIN
NUCLEI

Systemic AAV9
(4-8 x 10^{12} vg/mouse)

ddPCR, droplet digital PCR; LOD, logarithm of the odds (to the base of 10); TA, tibialis anterior; vg, viral genomes
Robinson-Hamm JN, et al. Presented at: 21st Annual Meeting of the American Society of Gene and Cell Therapy; May 16-19, 2018; Chicago, IL.

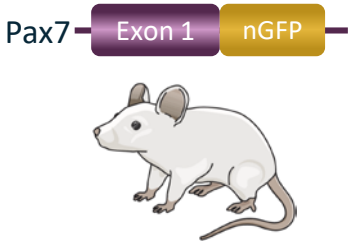
Satellite Cells Are the Stem Cells of Adult Muscle Tissue

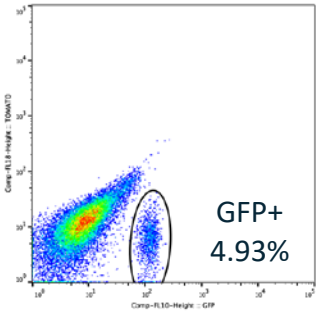


- Does AAV transduce satellite cells in vivo?
- Does CRISPR edit satellite cells in vivo?
- Does satellite cell editing facilitate long-term dystrophin restoration?

Cell Signaling Biology (2014).

AAV-CRISPR Editing of the Dystrophin Gene in Satellite Cells

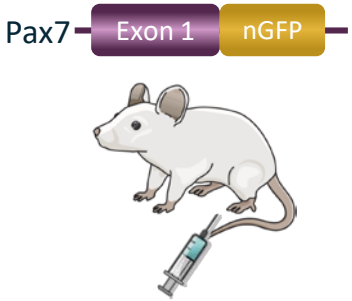


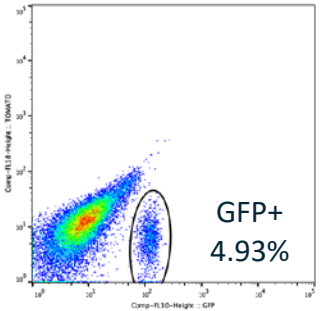


GFP, green fluorescence protein; nGFP, nuclear localized green fluorescence protein; PAX, Paired box protein.

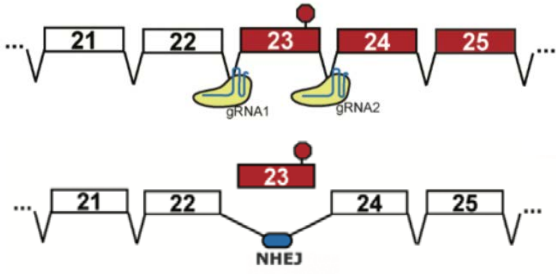
1. Kwon J and Gersbach CE, et al. Presented at: 21st Annual Meeting of the American Society of Gene and Cell Therapy; May 16-19, 2018; Chicago, IL.
2. Tabebordbar M, et al. *Science*. 2016;351(6271):407-441.

AAV-CRISPR Editing of the Dystrophin Gene in Satellite Cells





Targeting of Cas9 to introns 22 and 23 of DMD in nGFP mice



nGFP, nuclear localized green fluorescence protein.

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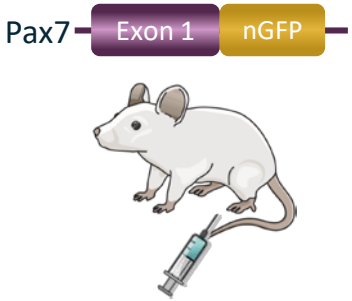

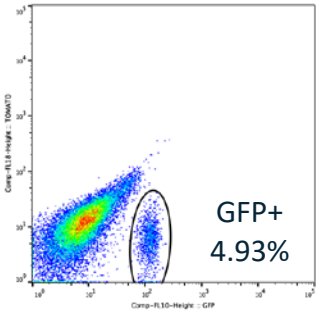

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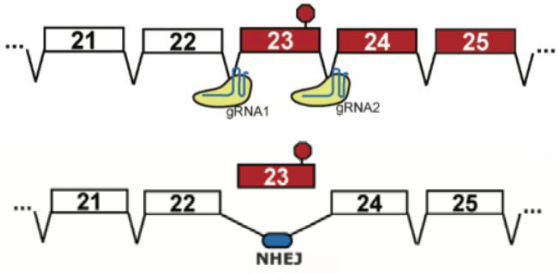
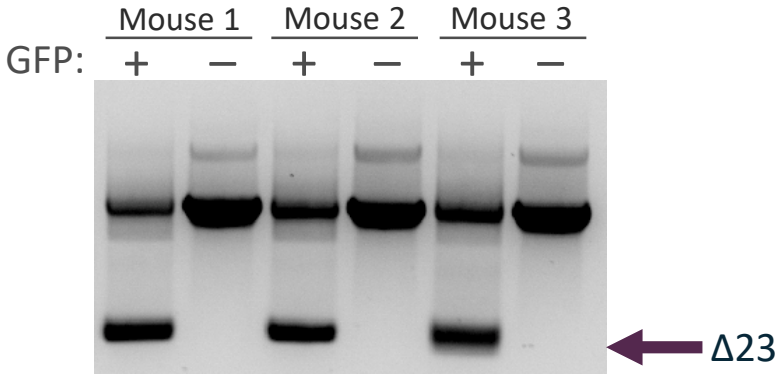
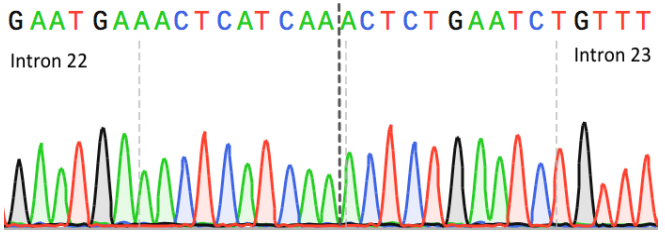


PCR Across Genomic Deletion Region



Sequencing of PCR Clones



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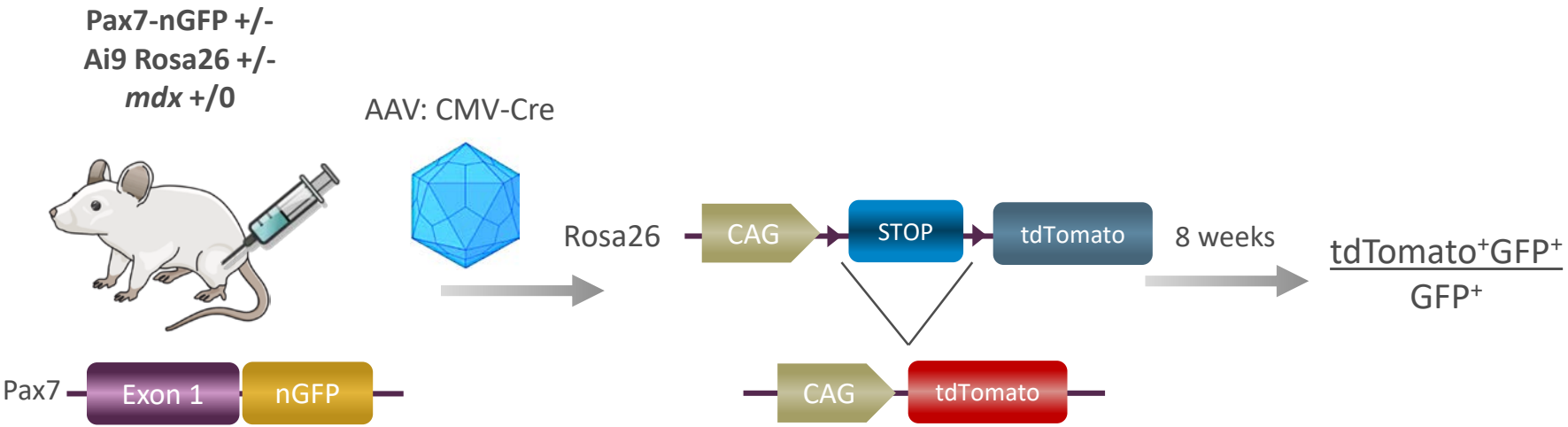
Systematic Assessment of AAV Transduction of Satellite Cells



Cre, CRE recombinase; td, tandem dimeric tomato.

1. Kwon J and Gersbach CE, et al. Presented at: 21st Annual Meeting of the American Society of Gene and Cell Therapy; May 16-19, 2018; Chicago, IL.
2. Tabebordbar M, et al. *Science*. 2016;351(6271):407-441.

Efficient Genetic Labeling of Satellite Cells by Multiple AAV Serotypes

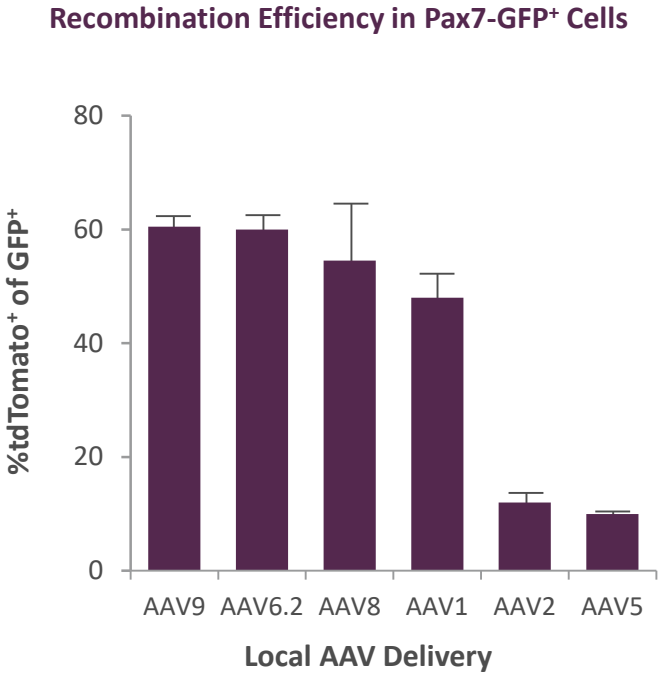
Recombination Efficiency in Pax7-GFP$^+$ Cells

n=5, mean + SEM; 8 weeks post-injections

SEM, standard error measure.

Kwon J and Gersbach CE. Presented at: 21st Annual Meeting of the American Society of Gene and Cell Therapy; May 16-19, 2018; Chicago, IL.

Efficient Genetic Labeling of Satellite Cells by Multiple AAV Serotypes



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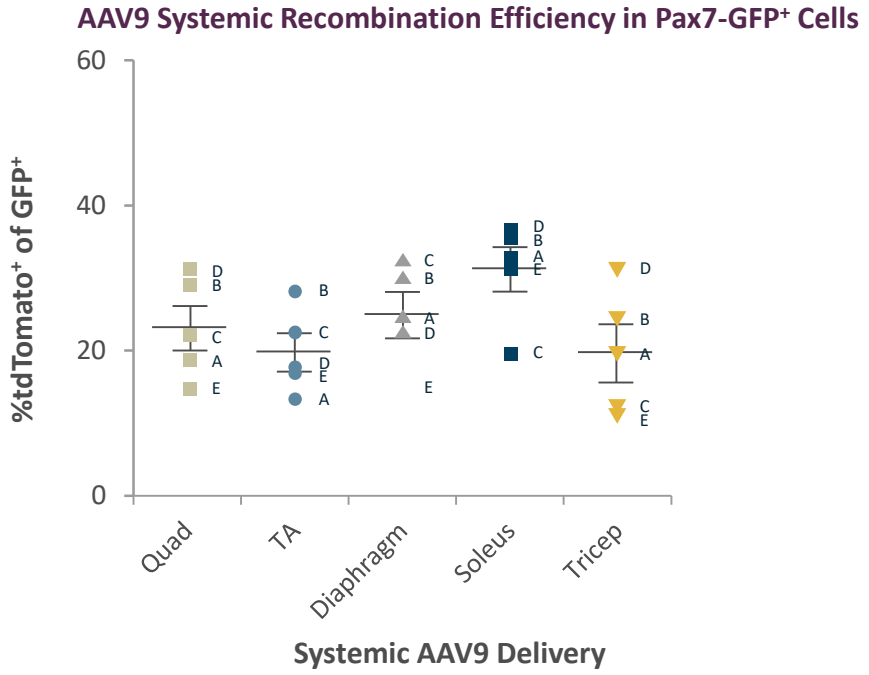

SEM, standard error measure.

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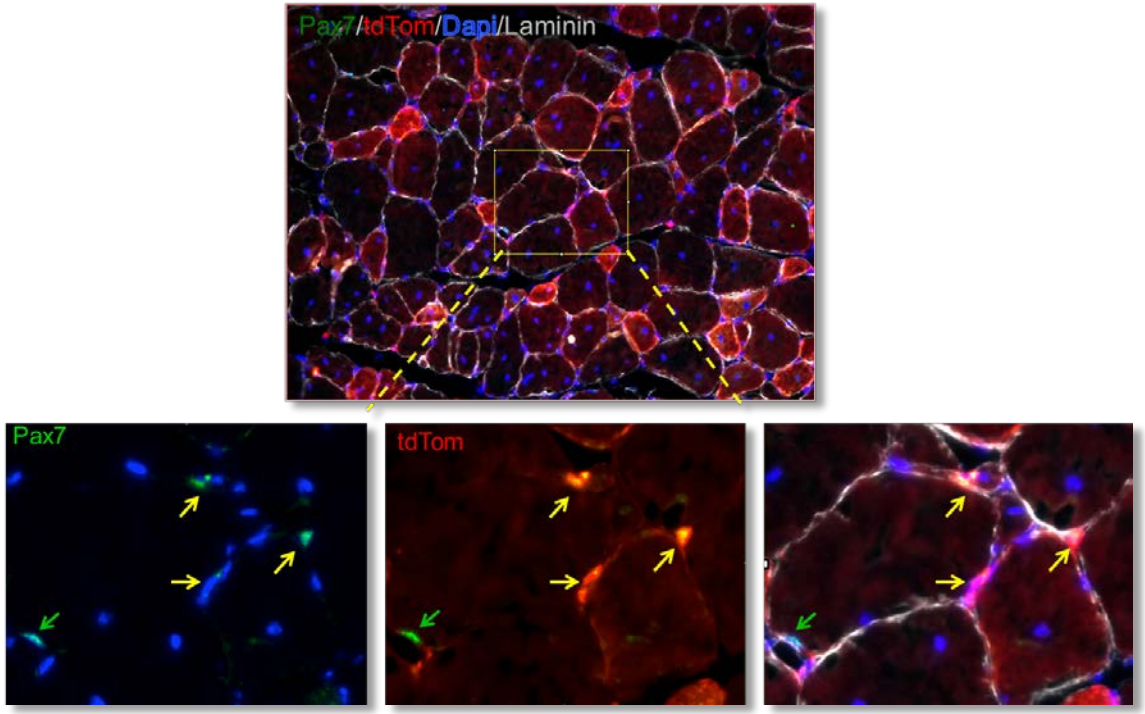

Kwon J and Gersbach CE. Presented at: 21st Annual Meeting of the American Society of Gene and Cell Therapy; May 16-19, 2018; Chicago, IL.

Summary

- Genome editing is an effective approach to restoring the endogenous dystrophin gene
- Exon excision provides flexibility in designing a safe and efficient editing strategy for the largest group of DMD patients
- AAV is an effective delivery vehicle for CRISPR-based genome editing
- Dystrophin editing and restoration is stable for at least 1 year
- A novel humanized mouse model of DMD enables preclinical development of human-targeted genome editing therapies
- AAV delivery leads to significant editing of muscle stem cells
- No toxicity or adverse events reported across many laboratories and study designs

Ongoing Efforts

- Optimizing vector and CRISPR design
- Scale-up to large animal studies
- Rigorous evaluation of safety and immunogenicity

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Annemeike Aartsma-Rus (Leiden)

Funding:

OUR VISION FOR THE FUTURE OF

Precision Genetic Medicine

SAREPTA THERAPEUTICS 2018 R&D DAY

Gene Therapy Approach for Treatment of Limb-Girdle Muscular Dystrophy (LGMD)

Louise Rodino-Klapac, PhD

Sarepta Therapeutics

Cambridge, MA

SAREPTA THERAPEUTICS

Myonexus THERAPEUTICS

Today's Presentation

- Introduction to LGMDs
- Shared therapeutic design principles among LGMD and DMD
- Historical clinical development for LGMD was guided by a stepwise approach
  - Intramuscular proof-of-concept studies
  - Vascular delivery
- Rational design for the use of AAVrh74 serotype and muscle-specific promoter
- Robust preclinical data led to approval of Phase 1 systemic study as first-in-human for LGMD

AAV, adeno-associated virus.

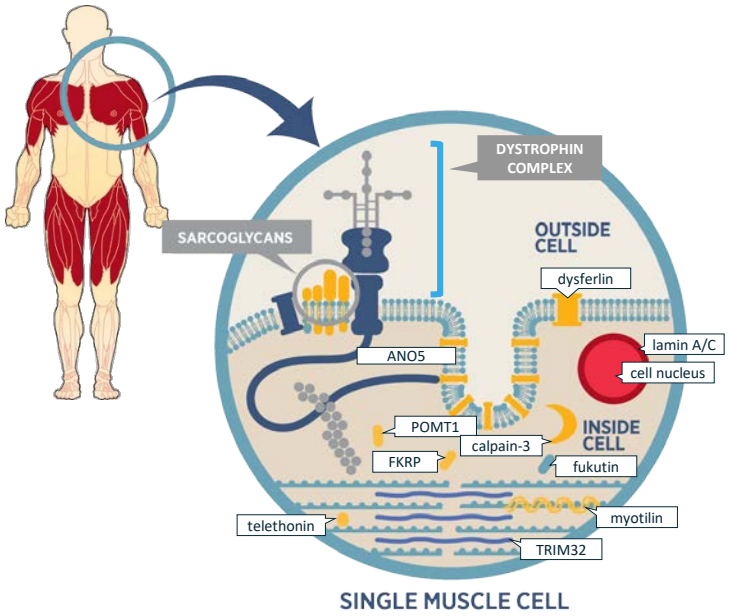
LGMDs Are Devastating Muscular Dystrophies

Autosomal recessive, monogenic, rare neuromuscular diseases that affect thousands globally

- LGMDs are progressive, debilitating muscle-wasting diseases with no therapies[1,2]
  - Affect males and females equally
  - Affect skeletal muscle
  - Affect cardiac muscle in some types
  - Elevated creatine kinase (CK) levels
  - Symptoms often develop before age 10
  - Loss of ambulation often in early teens
  - More severe forms mimic DMD
  - Death can result by age 30
- Consistent disease progression within each LGMD subtype
- Each of the ~20 LGMD subtypes is a rare disease
  - Prevalence estimate range: 1 in 14,500

1. NIH website. www.nih.gov. Accessed June 16, 2018.
2. MDA website. www.mda.org/disease/limb-girdle-muscular-dystrophy/causes-inheritance. Accessed June 16, 2018.

LGMDs Are Caused by Defects in the Proteins Comprising the Dystrophin-associated Protein Complex



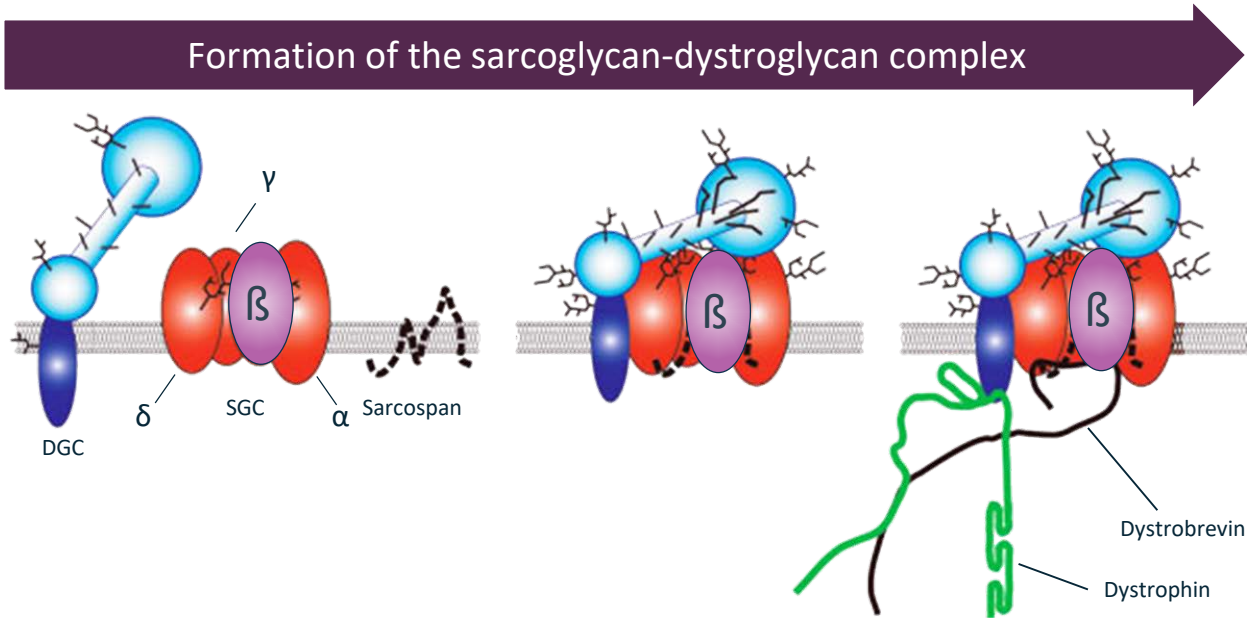
- **Sarcoglycans** prevent muscle damage during contraction
  - All 4 functional sarcoglycans must be present to form a functional sarcoglycan complex (SCG)
    - **Beta-sarcoglycan (MYO-101)**
    - **Alpha-sarcoglycan (MYO-102)**
    - **Gamma-sarcoglycan (MYO-103)**
  - Sarcoglycan deficiency leads to dystrophin deficiency
- **Dysferlin** and **ANO5** support muscle membrane repair (MYO-201 and MYO-301)
  - Failed muscle repair leads to chronic muscle degeneration

ANO5, anoctamin-5; FKRP, fukutin-related protein; POMT, protein-O-mannosyltransferase; TRIM, tripartite motif.

β-sarcoglycan (SGCB) Is the Fundamental Subunit of the Sarcoglycan Complex (SGC)

SGCB is the core of the SGC and binds to the dystroglycan complex (DGC)

- DMD and LGMD2E exhibit phenotypic similarities as a result of the biological dependence of dystrophin on the sarcoglycans, especially SGCB



Ozawa E, et al. *Muscle Nerve*. 2005;32(5):563-576.

Deep Pipeline of LGMD Gene Therapies

Targeting the most severe and common forms of LGMDs

Program	Indication	Gene	Preclinical	Phase 1 IM	Phase 1/2a ILP	Phase 1/2a IV
MYO-101[1]	LGMD2E	β-sarcoglycan				Initiate Q3 2018
MYO-102[2,3]	LGMD2D	α-sarcoglycan				
MYO-103	LGMD2C	γ-sarcoglycan				
MYO-201[2]	LGMD2B	Dysferlin				
MYO-301	LGMD2L	ANO5				

FDA, US Food and Drug Administration; ILP, isolated limb perfusion; IM, intramuscular; IV, intravenous.

1. For LGMD2E, the FDA granted permission to move directly to a systemic, IV delivery Phase 1/2a study; as a result, LGMD2E will move into systemic trials before other programs.
2. For LGMD2D and LGMD2B, the FDA required an initial intramuscular IM Phase 1 study to assess safety; dual-vector design.
3. For LGMD2D, the FDA required an isolated limb perfusion ILP Phase 1/2a study to further assess safety before progressing to a systemic, IV delivery Phase 1/2a study.

LGMDs Represent a Large Unmet Need

Single administration, corrective therapies combined with significant treatable patient populations

Indication	Prevalence[1] (per million)	US Population (321 million total)	EU Population (510 million total)	Rest of World Population (6670 million total)
LGMD2E	3.3	1100	1700	22,000
LGMD2D	3.5	1100	1800	23,000
LGMD2B	8.1	2600	4100	54,000
LGMD2C	2.0	640	1000	13,000
LGMD2L	5.5	1800	2800	37,000

1. Jain Foundation and Broad Institute data.

Shared Design Principles

- Systemic IV delivery is crucial to target all muscles
  - ***AAVrh74.MHCK7.Micro-dystrophin Paves the Way***
- Modular design decreases time for approval
- rh74 AAV was chosen due to superior skeletal muscle transduction in preclinical testing
  - Muscle cells do not divide → rh74 AAV transduced muscle fibers should be protected indefinitely
  - rh74 provides superior systemic delivery, including to the heart muscle
  - Preclinical data support single-administration hypothesis
- Promoters are optimized for the desired skeletal muscle and cardiac muscle expression levels
  - MHCK7 optimizes cardiac expression (LGMD2E and LGMD2B)
  - tMCK minimizes cardiac expression (LGMD2D)

MYO-101 (LGMD2E)
Beta-sarcoglycan

Program Synopsis

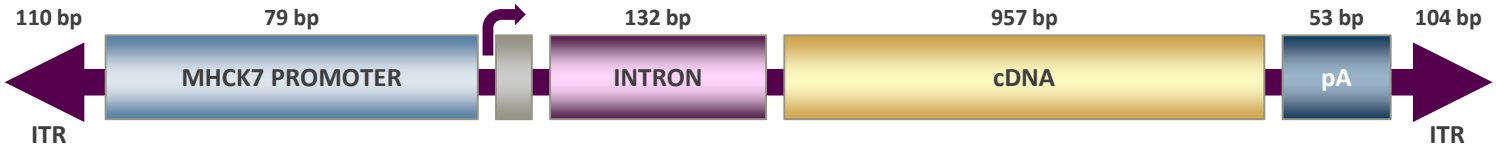
SAREPTA THERAPEUTICS

Myonexus THERAPEUTICS

MYO-101 (LGMD2E) Program Synopsis

LGMD2E mirrors a severe form of DMD, with significant cardiomyopathy and death in early adulthood

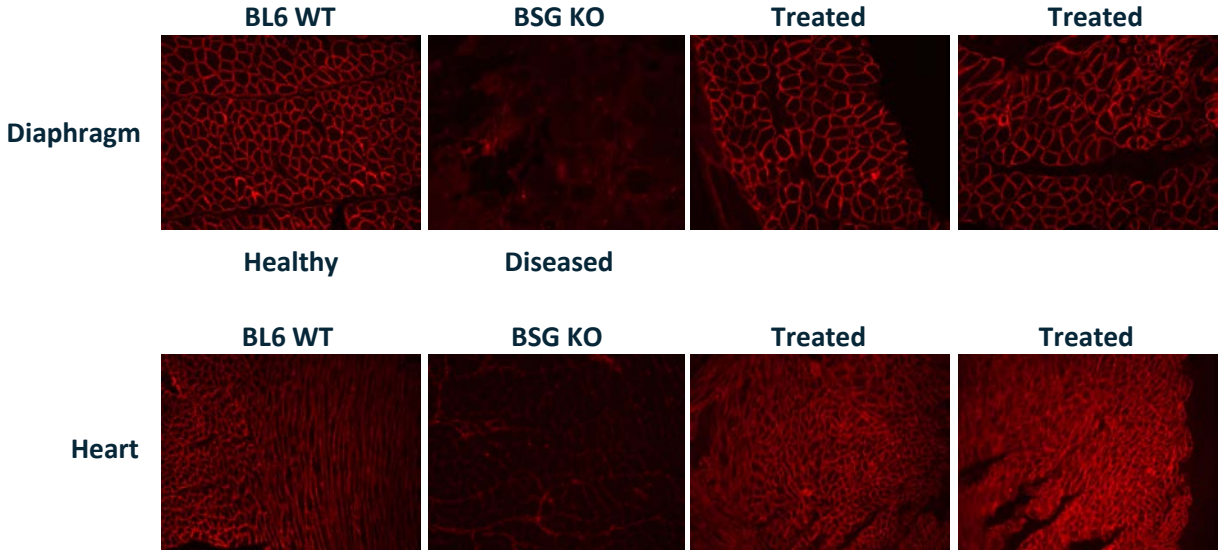
- Systemic delivery of the construct reconstitutes **full-length** β-sarcoglycan
  - **Self-complementary AAV vector** leads to 99% expression levels, restoring function in systemic mice efficacy studies
  - **No safety issues** were observed in preclinical safety studies
- Systemic Phase 1/2a IV trial starts in Q3 2018
  - 60-day biopsy data will be gathered in early 2019
- US Orphan Drug Designation application was granted in February 2018
- Rare Pediatric Disease Designation was granted in May 2018



bp, base pair; cDNA, complementary deoxyribonucleic acid; ITR, inverted terminal repeat.

Systemic Delivery Successfully Targets the Diaphragm and Myocardium in SGCB-/- Mice

Systemic delivery of the construct demonstrates >95% expression in the diaphragm and heart



BSG, β-sarcoglycan; KO, knockout; WT, wild type.
Pozsgai ER, et al. *Mol Ther.* 2017;25(4):855-869.

MYO-101 Preclinical Data

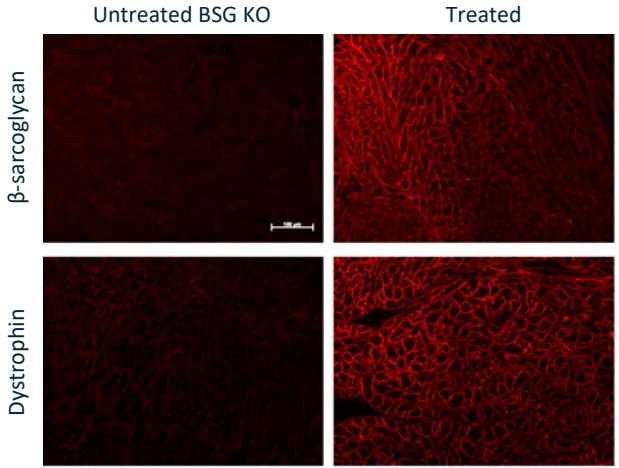
>95% β-sarcoglycan expression and dystrophin expression 6 months after treatment

Robust β-sarcoglycan Expression in Target Muscles

Muscle	Dose (vg Total Dose)	% Fibers Expressing β-sarcoglycan at 6 Months
Tibialis anterior	1×10^{12}	98.88 ± 0.55
Gastrocnemius	1×10^{12}	98.24 ± 0.82
Quadriceps	1×10^{12}	99.32 ± 0.19
Gluteal	1×10^{12}	97.50 ± 0.39
Psoas major	1×10^{12}	98.75 ± 0.23
Triceps	1×10^{12}	97.21 ± 1.35
Diaphragm	1×10^{12}	97.00 ± 1.26
Heart	1×10^{12}	≥95%

- Dose=IV delivery of 1×10^{12} vg/kg in mice (5×10^{13} vg/kg in humans)
- n=6 per group

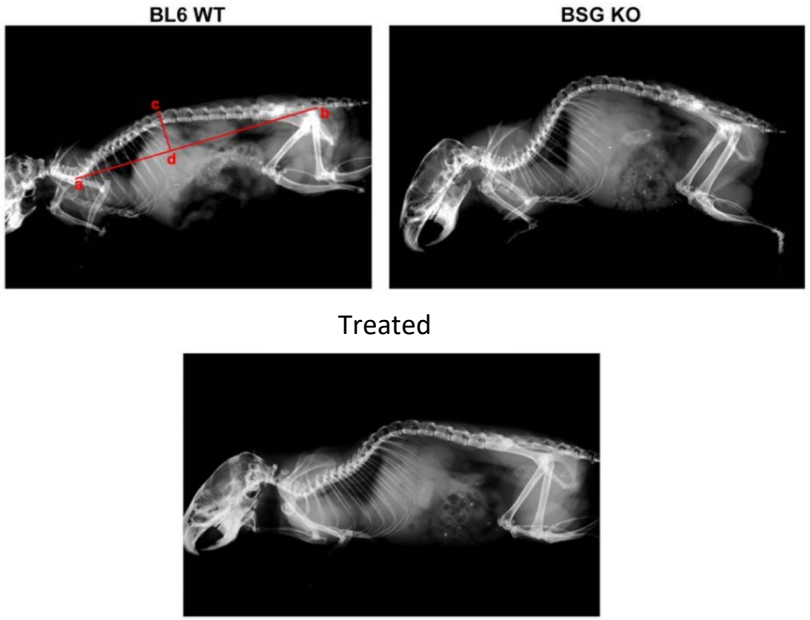
Restoration of Dystrophin-associated Protein Complex

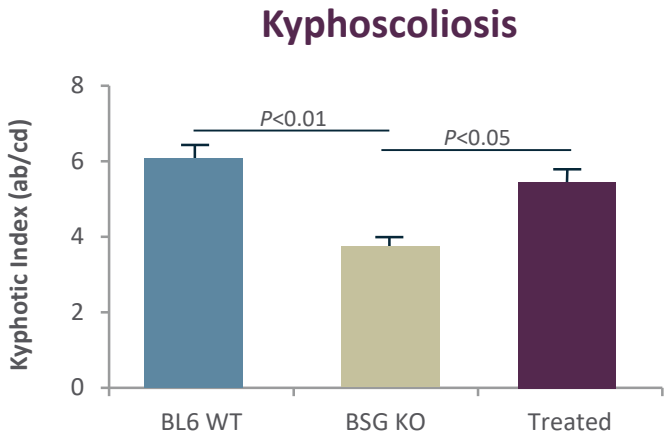


Pozsgai ER, et al. *Mol Ther*. 2017;25(4):855-869.

Systemic Delivery Reverses Scoliosis

Systemic delivery of the construct demonstrates increased muscle function and biomechanical benefits

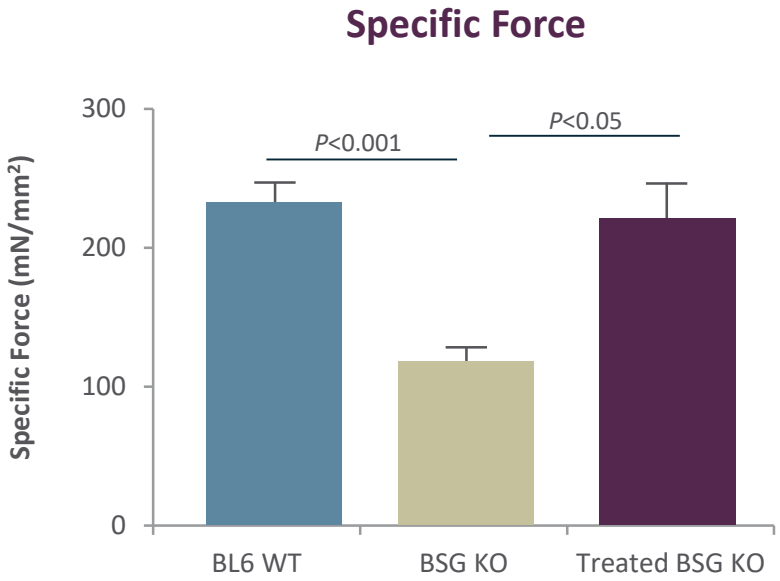


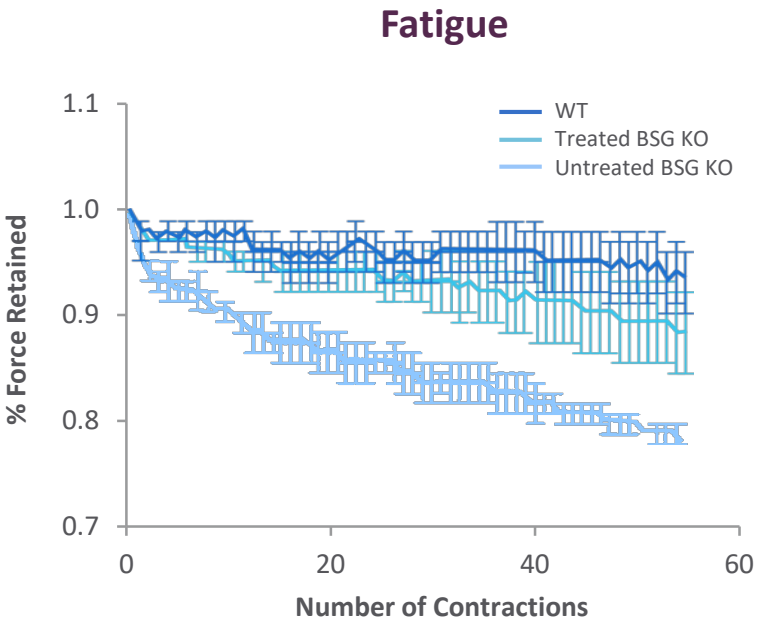


Pozsgai ER, et al. *Mol Ther*. 2017;25(4):855-869.

Systemic Delivery Restores Diaphragm Function

SGCB expression following systemic delivery of the construct restores diaphragm function in mice

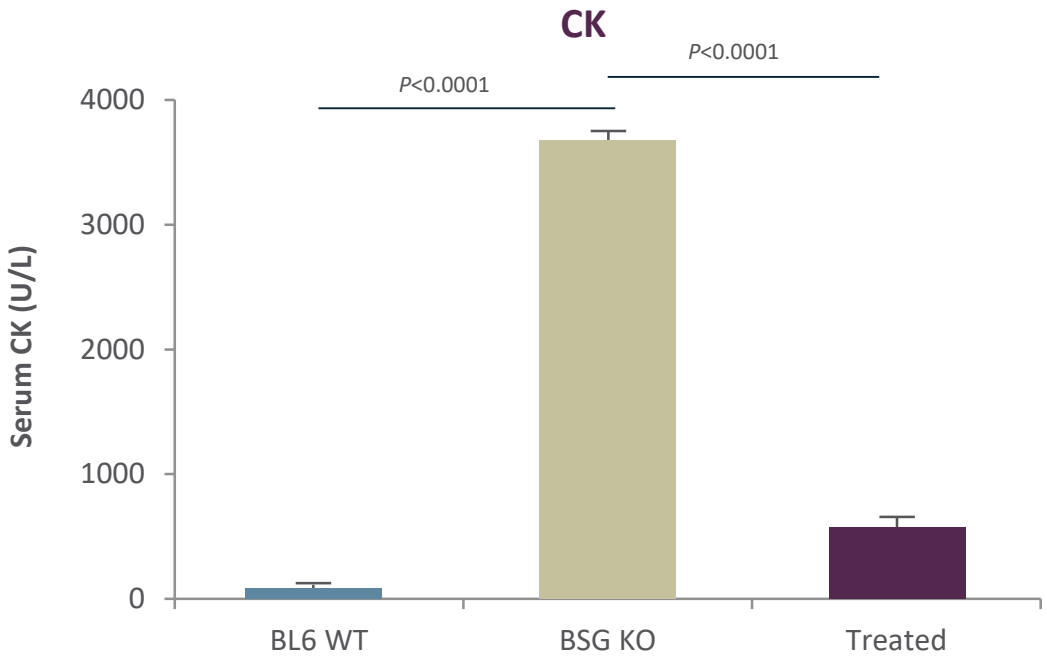




Pozsgai ER, et al. *Mol Ther*. 2017;25(4):855-869.

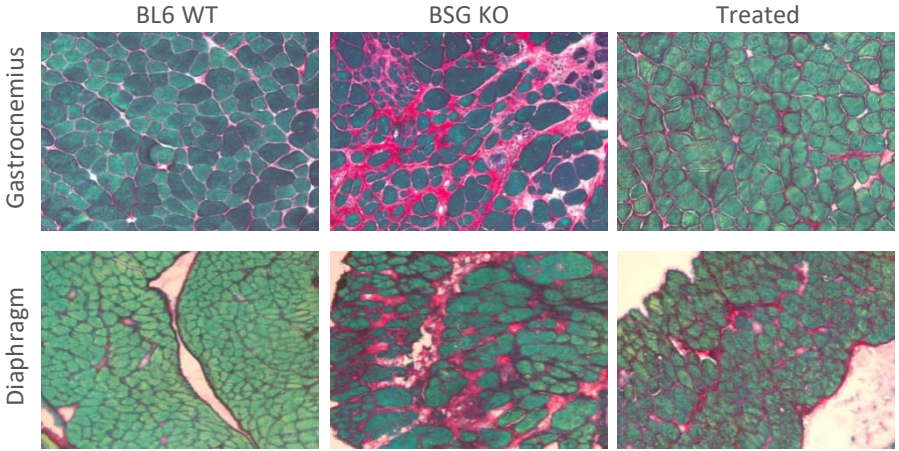
Systemic Delivery Reduces CK Levels

Systemic delivery of the construct reduces CK, a muscle damage biomarker (6 months)



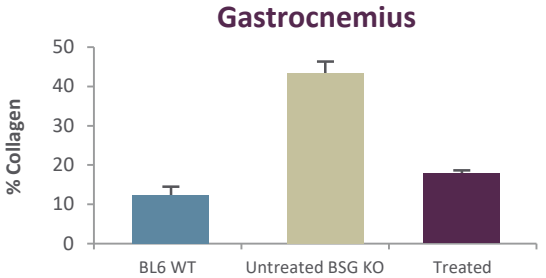
Systemic Delivery Reduces Muscle Fibrosis

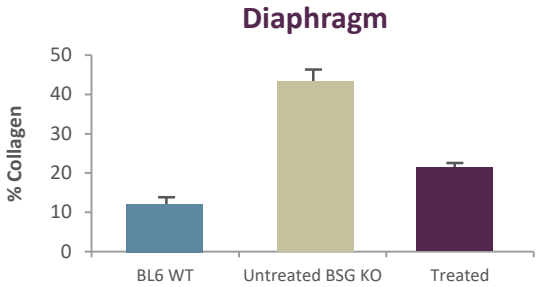
Systemic delivery of the construct prevents fibrosis in addition to improving muscle function in mice



Green: Muscle

Pink: Fibrosis/Scar Tissue





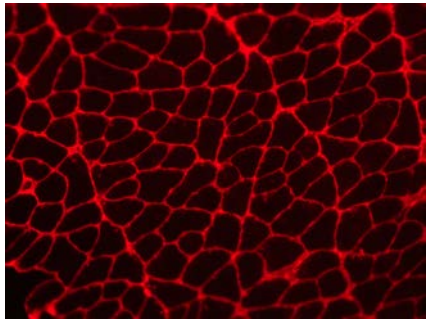
Pozsgai ER, et al. *Mol Ther*. 2017;25(4):855-869.

Durability: Sustained Expression for Lifespan of Mouse – 27 Months

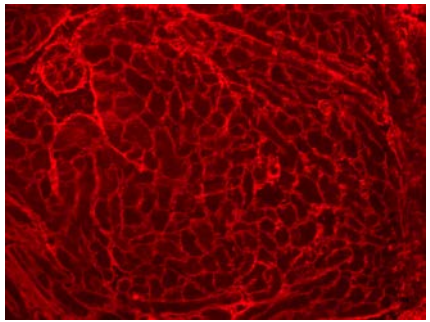
Robust β-sarcoglycan Expression in Target Muscles

Muscle	Dose (vg Total Dose)	% Fibers Expressing β-sarcoglycan at 27 Months
Tibialis anterior	1×10^{12}	99.9
Gastrocnemius	1×10^{12}	99.8
Quadriceps	1×10^{12}	98.7
Gluteal	1×10^{12}	99.7
Psoas major	1×10^{12}	99.0
Triceps	1×10^{12}	99.3
Diaphragm	1×10^{12}	95.9
Heart	1×10^{12}	≥95%

- Dose=IV delivery of 1×10^{12} vg/kg in mice (5×10^{13} vg/kg humans)



Skeletal Muscle



Heart

MYO-101 (LGMD2E) IV Phase 1/2a Design

Cohort 1 60-day biopsy data in early 2019

Protocol Synopsis

- Randomized, double-blind, placebo-controlled
- Single IV infusion of the construct or placebo
  - 9 subjects: 2 cohorts, 2 dose levels
  - 2:1 active:placebo cohort 1 @ 5 x 10^{13} vg/kg
  - 4:2 active:placebo cohort 2 @ 2 x 10^{14} vg/kg if <50% fiber expression
  - 3 placebo crossovers after 1-year reading of Subject 9
- **Primary**
  - Safety
  - Gene expression (≥20% of muscle fibers expressing β-sarcoglycan vs baseline)
- **Secondary** (functional)
  - 100-meter time, workspace volume, 6MWT, NSAA, MVIC, testing of knee extensors and flexors, cardiac ejection fraction by MRI, TUG, ascend 4 stairs

6MWT, 6-meter walk test; MRI, magnetic resonance imaging; MVIC, Maximum Voluntary Isometric Contraction; NSAA, North Star Ambulatory Assessment; TUG, timed up and go.

MYO-102 (LGMD2D)
Alpha-sarcoglycan

Program Synopsis

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Myonexus THERAPEUTICS

LGMD2D (α-sarcoglycan): MYO-102 Program Synopsis

Isolated limb perfusion Phase 1/2a proof-of-concept study demonstrated systemic safety and protein expression

- First Phase 1 IM Proof-of-concept Study
  - Demonstrated safety and expression of α-sarcoglycan
- ILP Phase 1/2a completed in Q4 2017
  - Construct delivered in one or both lower limbs to establish safety basis for systemic trials
  - Demonstrated systemic exposure safety and expression of α-sarcoglycan
  - α-sarcoglycan was present in all muscle biopsies 6 months after treatment
  - α-sarcoglycan expression increased vs baseline in all biopsies
- Systemic delivery of the construct in mice reconstitutes full-length α-sarcoglycan
  - Restores function in preclinical efficacy studies
  - No safety issues observed in preclinical safety studies
- Protocol update enabling systemic, IV delivery Phase 1/2a trial planned in 2018

MYO-102 IM Phase 1 Clinical Data

Initial Study, Single Injection Into Foot

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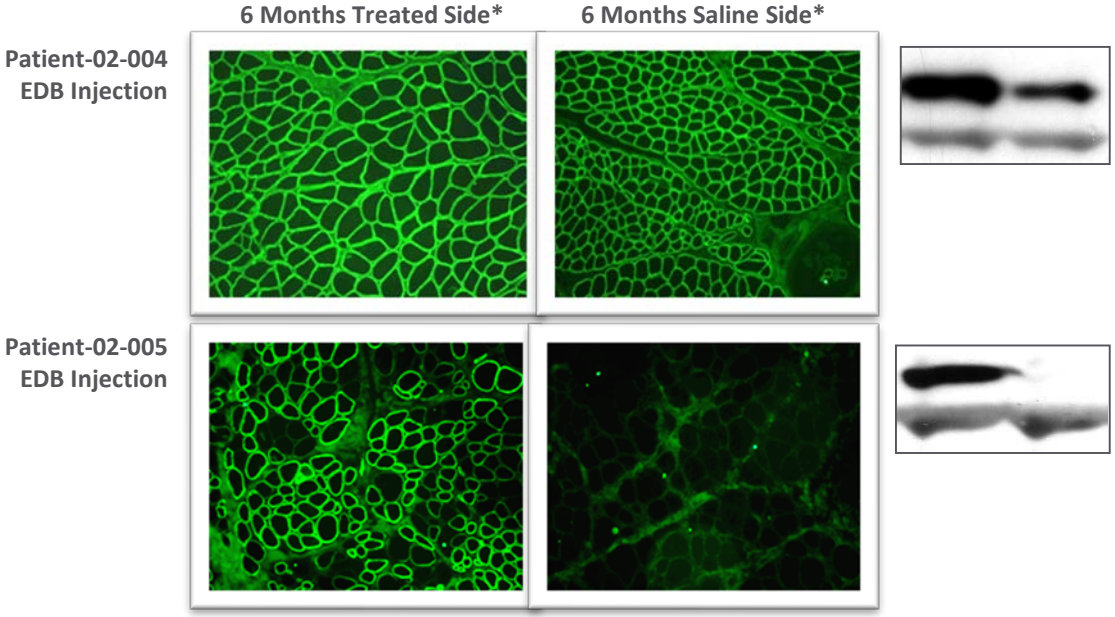
LGMD2D (α-sarcoglycan) IM Phase 1 Demonstrated Expression

6 subjects treated with sustaining expression assessed at 6, 12, and 24 weeks

α-sarcoglycan Expression Levels in Treated and Saline (Untreated) Muscles

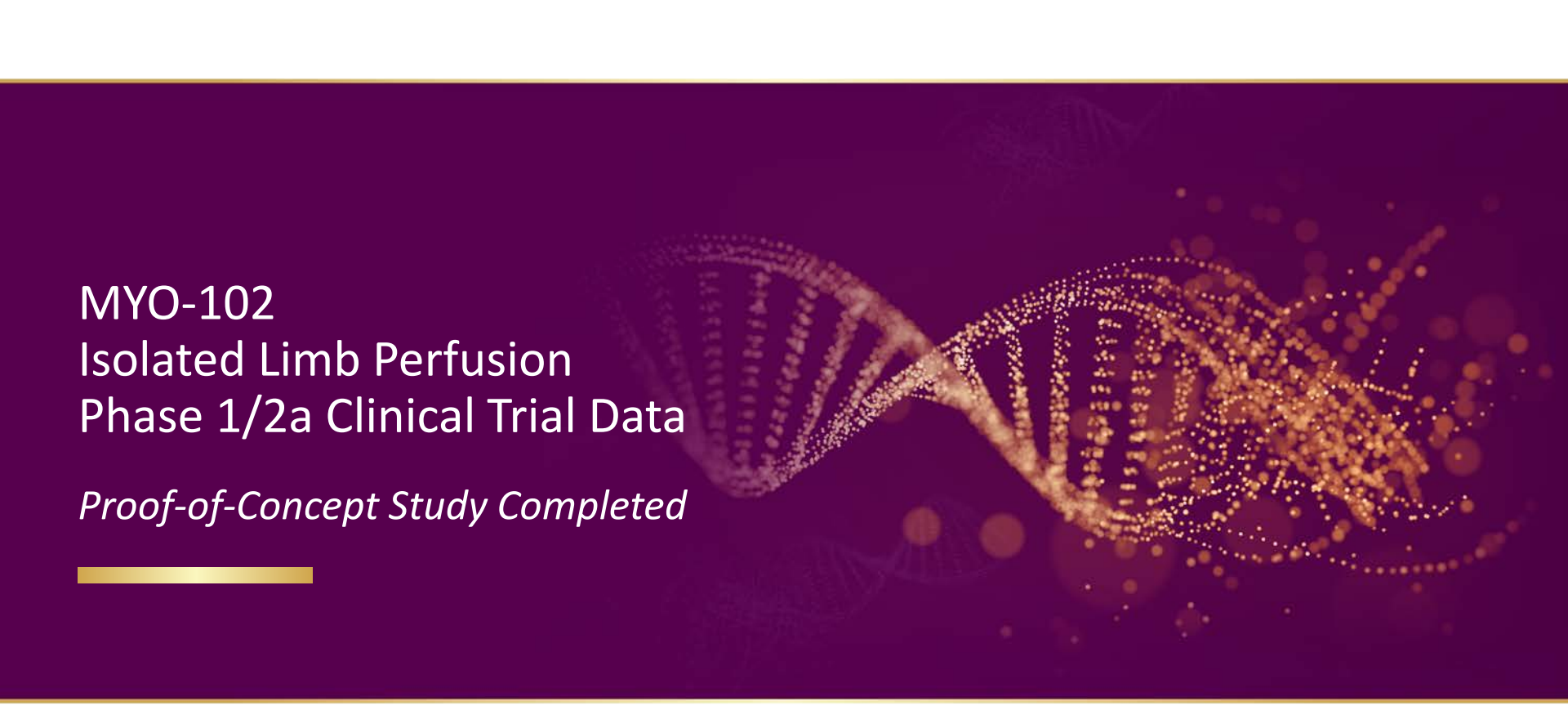


- Fiber size increased from 28.2 ± 1.1 µm to 52.2 ± 13.1 µm

EDB, extensor digitorum brevis.
*20x magnification.

MYO-102
Isolated Limb Perfusion
Phase 1/2a Clinical Trial Data

Proof-of-Concept Study Completed



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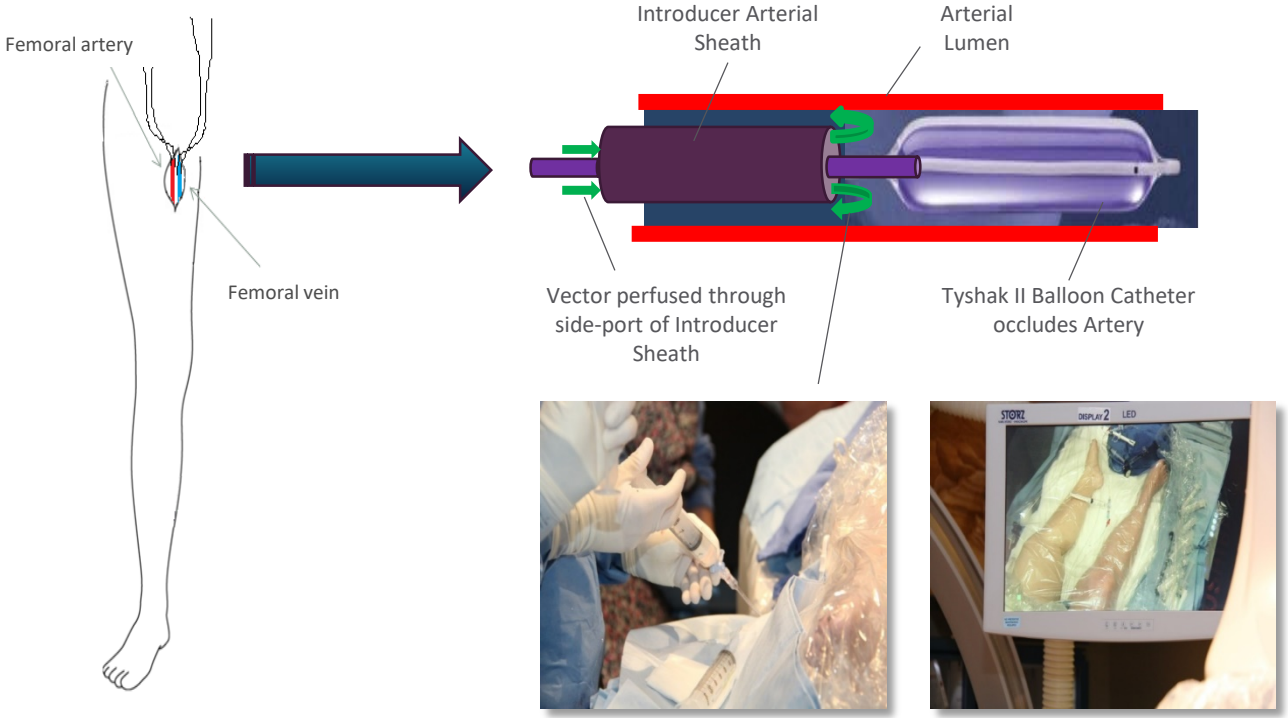
MYO-102 ILP Phase 1/2a Study Procedure

Gene transfer clinical trial for LGMD2D (α-sarcoglycan deficiency) (NCT01976091)



LGMD2D ILP Phase 1/2a Study Measures

Gene transfer clinical trial for LGMD2D (α-sarcoglycan deficiency) (NCT01976091)

Primary Outcome Measures

- Time frame: 2 years
- Safety with fewer than one grade 3 adverse event or two grade 2 adverse events
- Safety endpoints assessed by changes in hematology, serum chemistry, urinalysis, immunologic response to rAAVrh.74 and hSGCA, and reported history and observations of symptoms

Secondary Outcome Measures

- Time frame: 2 years
- Efficacy measured by the 6-minute walk test and direct muscle testing for strength by MVIC
- Quantitative measures at baseline; Days 30, 60, 90, and 180; and at the end of the 1st and 2nd years
- Subjects evaluated at baseline; infusion visit (Days 0-2); and at follow-up visits on Days 7, 14, 30, 60, 90, and 180

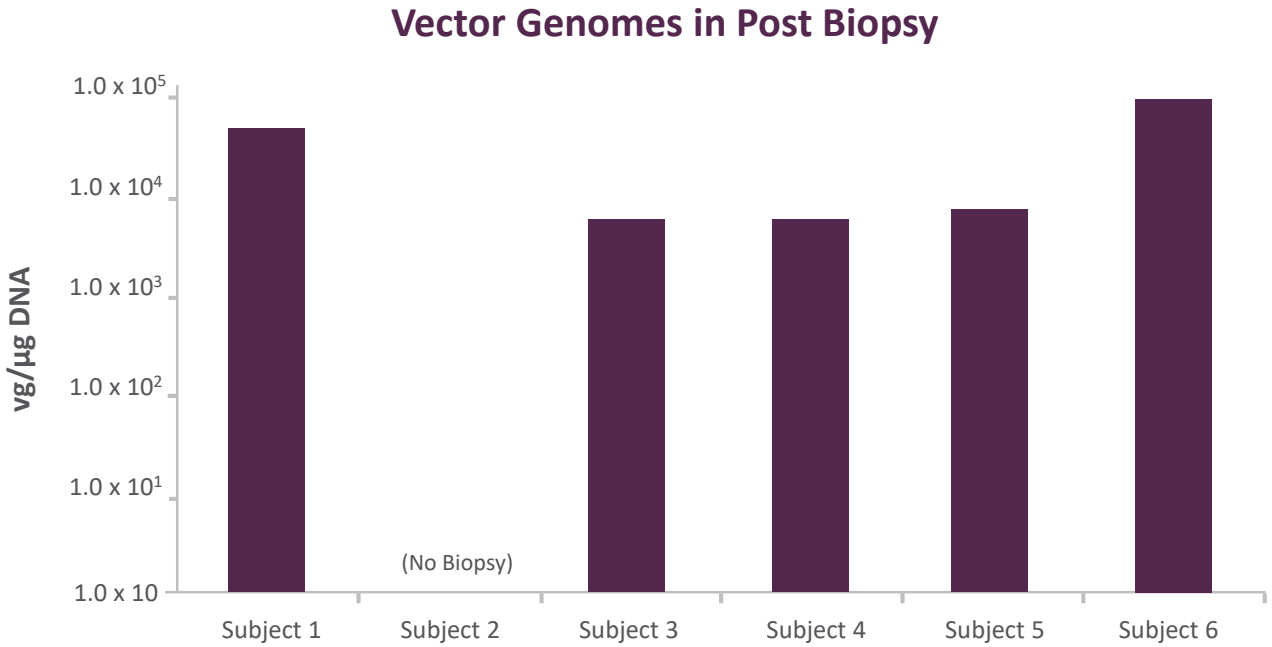
MYO-102 (LGMD2D) ILP Phase 1/2a Study

Gene transfer clinical trial for LGMD2D (α-sarcoglycan deficiency) (NCT01976091)

Patient	Ambulatory	Dose	% of Predicted Efficacious Dose	Expression
1	No (single limb)	1 x 10^{12} vg/kg	2% (1/50th)	Tibialis anterior: 17% higher in right vs left (25% of normal)
2	Yes (dual limb)	1 x 10^{12} vg/kg	2% (1/50th)	No biopsy due to fall and fracture
3	Yes (dual limb)	1 x 10^{12} vg/kg	2% (1/50th)	Quadricep: 38% increase from baseline (14% of normal)
4	Yes (dual limb)	1 x 10^{12} vg/kg	2% (1/50th)	Quadricep: 12.5% increase from baseline (16% of normal)
5	Yes (dual limb)	3 x 10^{12} vg/kg	10% (1/10th)	Quadricep: 22% increase from baseline (15% of normal)
6	Yes (dual limb)	3 x 10^{12} vg/kg	10% (1/10th)	172% increase from baseline Tibialis anterior: 21.5% of normal Quadricep: 25.7% of normal

- One-time vector infusion to an isolated lower limb with a 10-minute dwell time
- FDA required very conservative doses, including first patient to be nonambulatory
- On Day 180, a muscle biopsy on the injected muscles was done in one leg to compare with the pretreatment biopsy done at baseline screening in the opposite leg

Vector DNA Present in All Biopsies 6 Months Post Gene Delivery



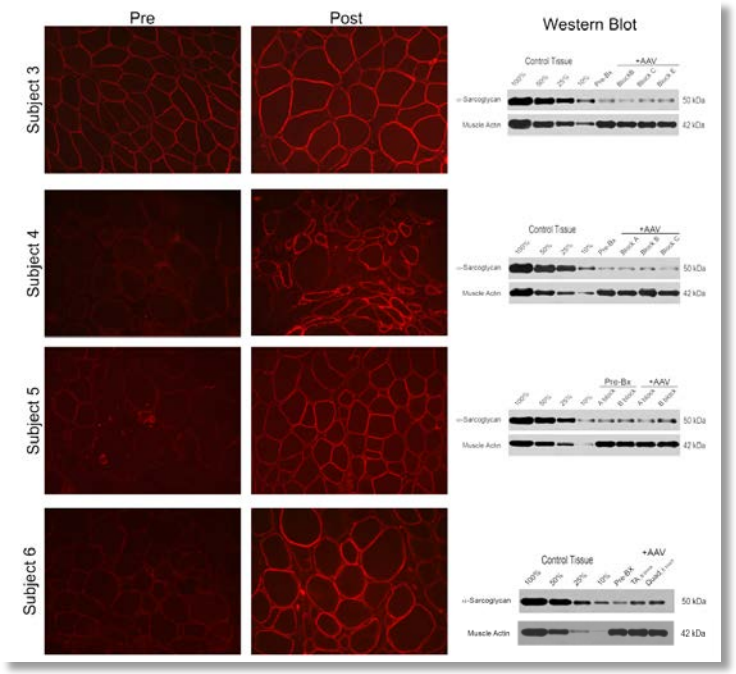
Increased α-Sarcoglycan Expression in Quadriceps and Tibialis Anterior

Subject 3
- Quadriceps muscle biopsy (see image)
- 38% increase from baseline (14% of normal)

Subject 4
- Quadriceps muscle biopsy (see image)
- 12.5% increase from baseline (16% of normal)

Subject 5
- Quadriceps muscle biopsy (see image)
- 22% increase from baseline (15% of normal)

Subject 6
- Biopsy of tibialis anterior and quadriceps (see quad image)
- 172% increase from baseline
- 21.5% of normal in tibialis anterior and 25.7% of normal in quadriceps



Preclinical Bridging Data for IV Delivery

Intend to Submit Amended Protocol to FDA in H1 2018

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12-week Safety and Efficacy Study Design

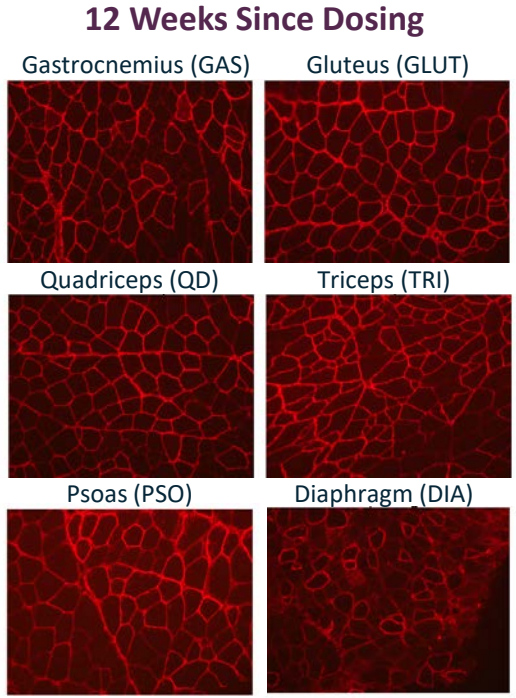
Required preclinical bridging study to amend IND protocol

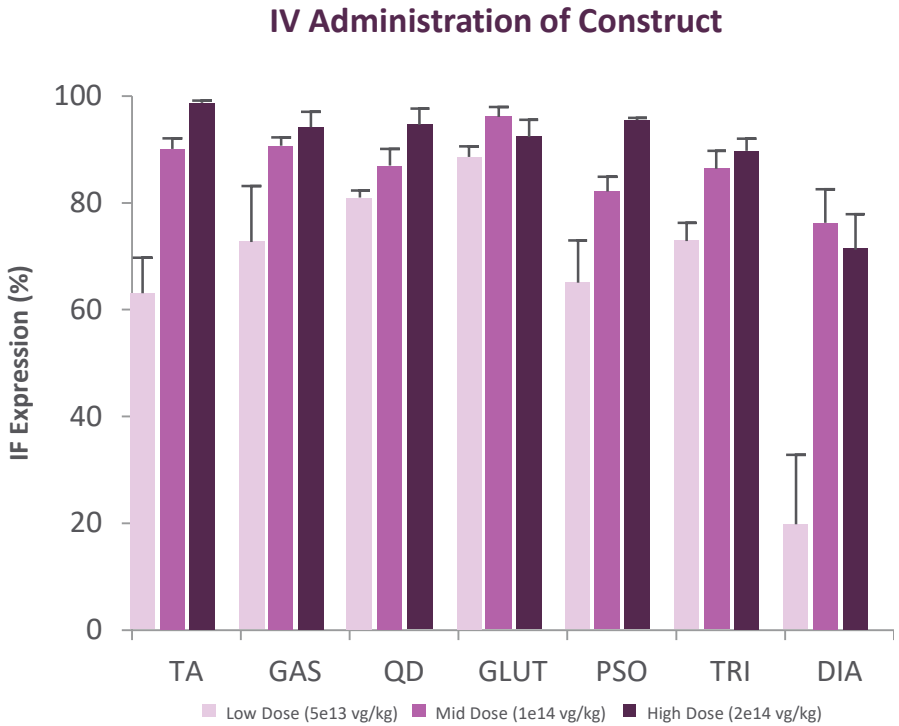
Mouse Strain	Test Article	Human Dose	Sample Size	Endpoint
C57/BL6	Lactated Ringer's injection*	NA	6	12 weeks
SGCA KO	Lactated Ringer's injection*	NA	6	12 weeks
SGCA KO	Construct	5×10^{13} vg/kg	6	12 weeks
SGCA KO	Construct	1×10^{14} vg/kg	6	12 weeks
SGCA KO	Construct	2×10^{14} vg/kg	6	12 weeks

- Following 12 weeks of treatment, endpoint analysis was performed in the following order:
  - Clinical chemistries, including CK, open-field activity monitoring, diaphragm and tibialis anterior muscle physiology, necropsy, immunofluorescence for α-sarcoglycan with quantification, Western blot, muscle morphometrics, and formal histopathology. Animals were dosed at 4 to 5 weeks of age

*USP, a source of water and electrolytes or as an alkalinizing agent.
IND, investigational new drug; NA, not applicable.

Muscle Fiber Expression Demonstrates a Dose-dependent Response

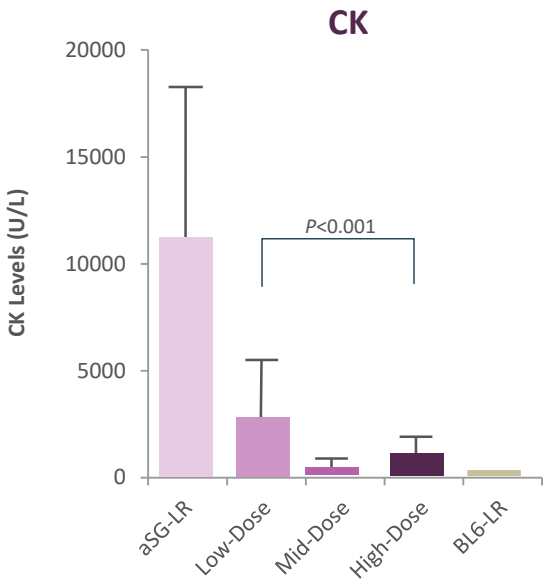


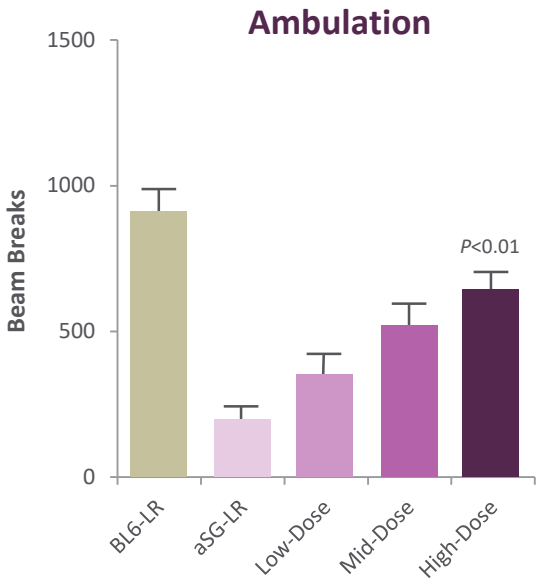


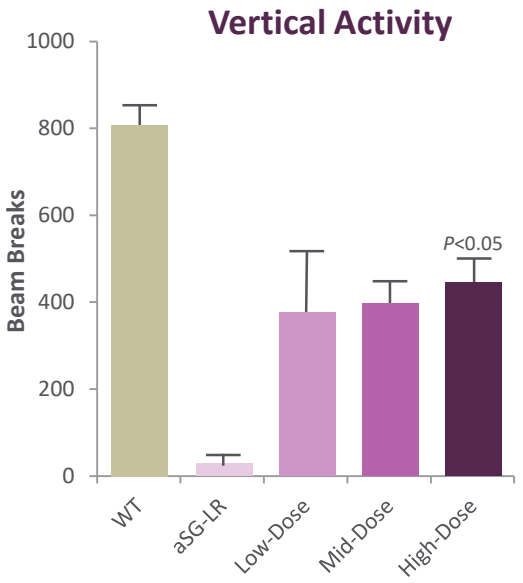
IF, immunofluorescence; TA, tibialis anterior.

*1 x 10^{12} vg/kg in mice = 5 x 10^{13} vg/kg in humans – representative images.

CK Levels and Physical Activity Are Significantly Improved

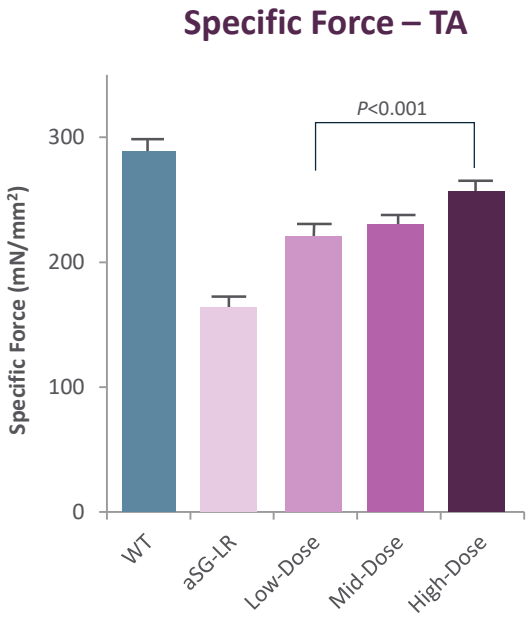


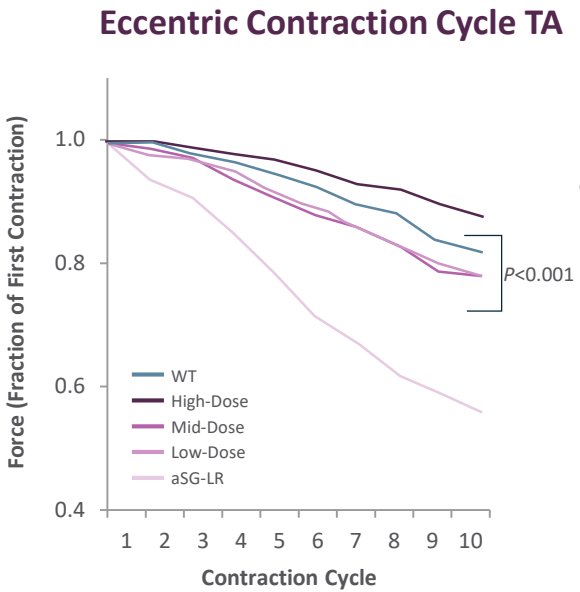


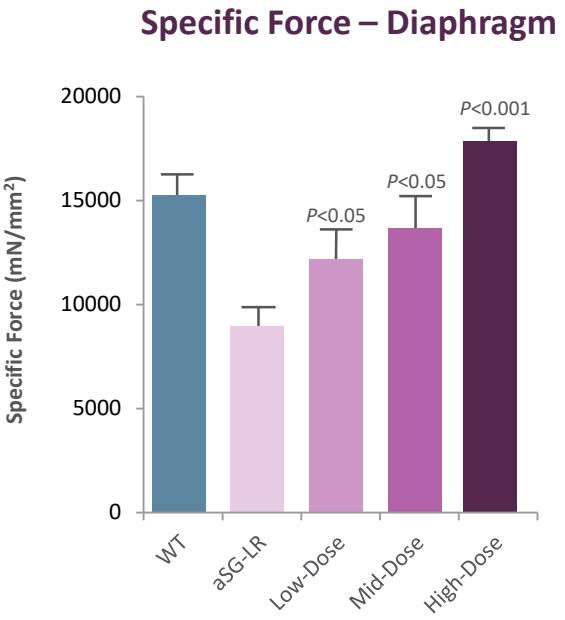


aSG-LR, alpha sarcoglycan locoregional; LR, locoregional.

Tibialis Anterior and Diaphragm Show Increase in Muscle Strength and Muscle Stamina







MYO-102 (LGMD2D) IV Phase 1/2a Design

Dose escalation and outcome measure learnings will inform Phase 2/3 design and successive programs' design

Protocol Synopsis

- Randomized, double-blind, placebo-controlled
- Single IV infusion of construct or placebo: 2 cohorts, 2 dose levels
  - 2:1 active:placebo cohort 1 @ 5 x 10^{13} vg/kg
  - 6:3 active:placebo cohort 2 @ 2 x 10^{14} vg/kg if <50% fiber expression
  - Placebo crossover after 1-year reading from last patient dosed
- **Primary**
  - Safety
  - Gene expression (≥20% of muscle fibers expressing α-sarcoglycan vs baseline)
- **Secondary** (functional)
  - 100-meter time, workspace volume, 6MWT, NSAA, MVIC, testing of knee extensors and flexors, cardiac ejection fraction by MRI, TUG, ascend 4 stairs

MYO-103 (LGMD2C)
Gamma-sarcoglycan

Program Synopsis

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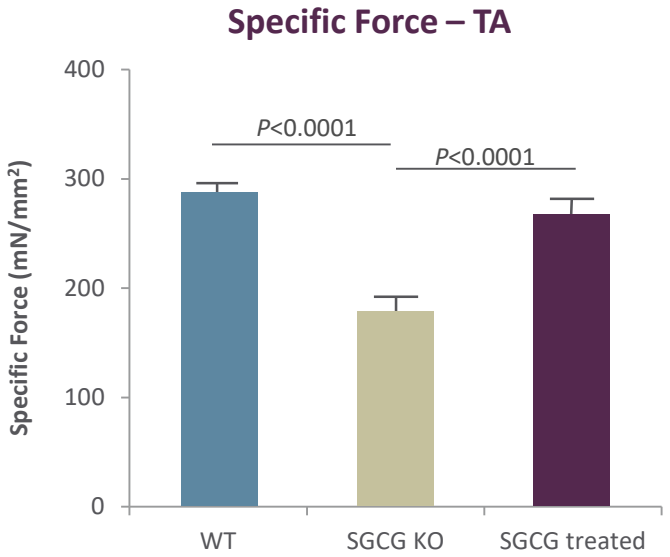
Myonexus THERAPEUTICS

MYO-103 Preclinical Status

Pre-IND meeting expected mid-2018 to align on preclinical safety package

Robust γ-sarcoglycan Expression in Target Muscles Normalizes Force

Muscle	Dose (vg Total Dose)	% Fibers Expressing γ-sarcoglycan at 3 Months
Tibialis anterior	1 x 10^{12}	98.17
Gastrocnemius	1 x 10^{12}	89.41
Quadriceps	1 x 10^{12}	88.95
Gluteal	1 x 10^{12}	95.27
Psoas major	1 x 10^{12}	88.38
Triceps	1 x 10^{12}	96.45
Diaphragm	1 x 10^{12}	89.19
Heart	1 x 10^{12}	≥95%



MYO-103 Pivotal Preclinical Studies Ongoing

12-week safety and dose-ranging study in KO mice

Mouse Strain	Test Article	Human Dose	Sample Size	Endpoint
C57/BL6	Lactated Ringer's Injection*	NA	6	12 weeks
SGCG KO	Lactated Ringer's Injection*	NA	6	12 weeks
SGCG KO	Construct	5×10^{13} vg/kg	6	12 weeks
SGCG KO	Construct	1×10^{14} vg/kg	6	12 weeks
SGCG KO	Construct	2×10^{14} vg/kg	6	12 weeks

- Following 12 weeks of treatment, endpoint analysis is performed in the following order
  - Clinical chemistries, including CK, open-field activity monitoring, diaphragm and tibialis anterior muscle physiology, necropsy, immunofluorescence for γ-sarcoglycan with quantification, Western blot, muscle morphometrics, formal histopathology. Animals dosed at 4-5 weeks of age
- Pre-IND meeting request in mid-2018

*USP, a source of water and electrolytes or as an alkalinizing agent.

MYO-201 (LGMD2B)
Dysferlin

Program Synopsis

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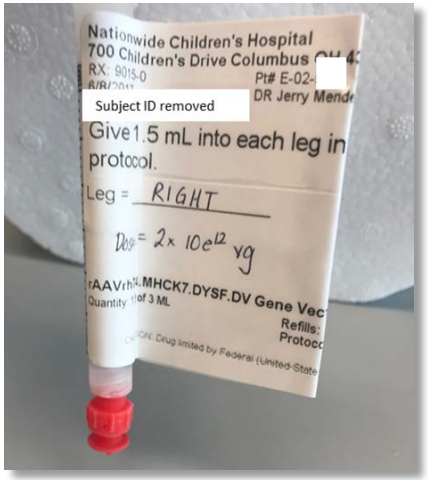
Myonexus THERAPEUTICS

MYO-201 (LGMD2B) Program Synopsis

US Orphan Designation granted in 2016; positive Phase 1 IM safety and gene expression proof-of-concept data

- Phase 1 IM trial (NCT02710500) ongoing
  - Construct delivery to EDB muscle to assess safety and expression of dysferlin protein
  - Promising interim results, demonstrating safety and protein expression
- In preclinical models, systemic delivery reconstitutes full-length dysferlin
  - Dual vector delivered in equal amounts
  - No safety issues observed in preclinical safety studies
  - Sustained protein expression and functional improvements observed for 15+ months in mice (until natural death)
- Protocol enabling systemic, IV delivery Phase 1/2a trial to be submitted



MYO-301 (LGMD2L)
Anoctamin-5

Program Synopsis

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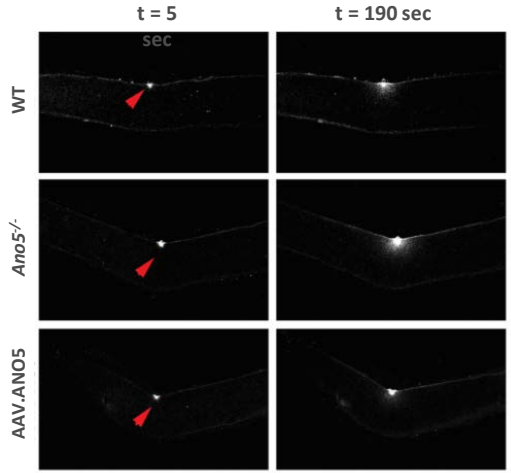
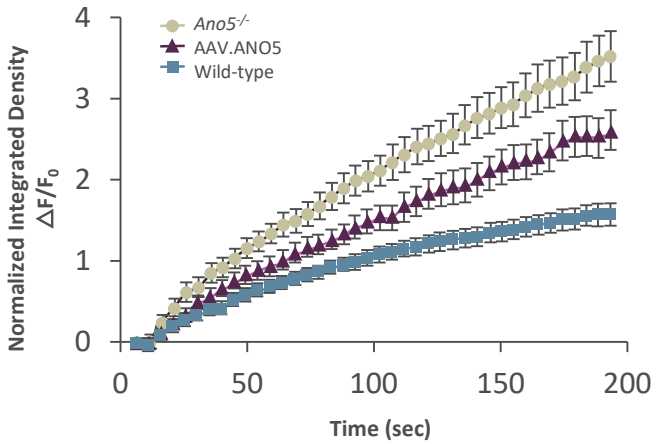
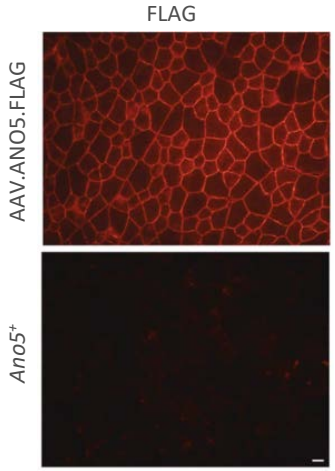
Myonexus THERAPEUTICS

MYO-301 LGMD2L (ANO5 Deficiency) Preclinical Progress

- Generated and characterized *ANO5* KO mouse
- Demonstrated ANO5 expression following delivery of construct
- ANO5 expression improved membrane repair capability and regeneration response
- Formal safety and dose-ranging studies underway







Griffin DA, et al. *Hum Mol Genetics*. 2016;25(10):1900-1911.

Summary

- LGMDs represent a significant unmet need
- Myonexus LGMD programs target ~70% of the LGMD population with current pipeline
- Shared design principles (AAVrh74 and promoters) increase efficiency between programs
- A Phase 1/2 study for LGMD2E (β-sarcoglycan) will be the first systemic gene therapy trial for LGMD
  - Preliminary results expected Q1 2019

OUR VISION FOR THE FUTURE OF

Precision Genetic Medicine

SAREPTA THERAPEUTICS, INC 2018 R&D DAY

The Chemical Architecture of PPMO

Gunnar J. Hanson, PhD

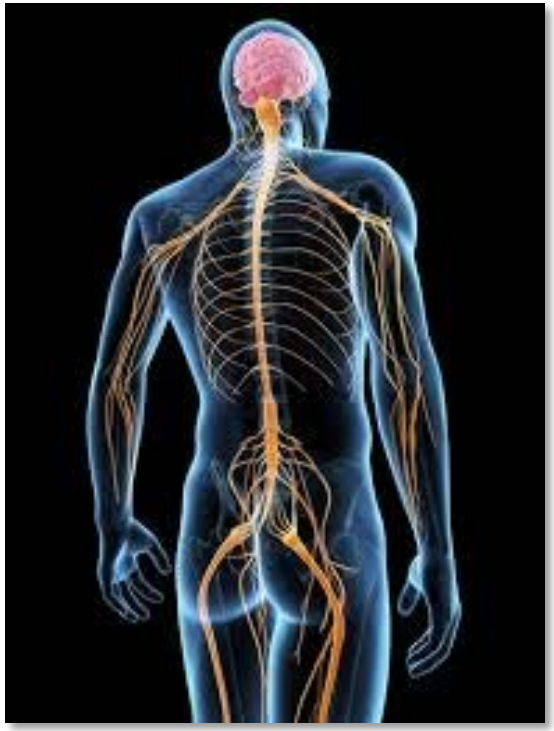
Senior Director of Research Chemistry

Sarepta Therapeutics

Cambridge, MA

Phosphorodiamidate Morpholino Oligomers (PMOs) Target Rare Diseases

- Muscular, neuromuscular, and central nervous system diseases represent a vast range of progressive, life-threatening disorders, most of which have no cure
- We have chosen PMO as the basis for our medicines



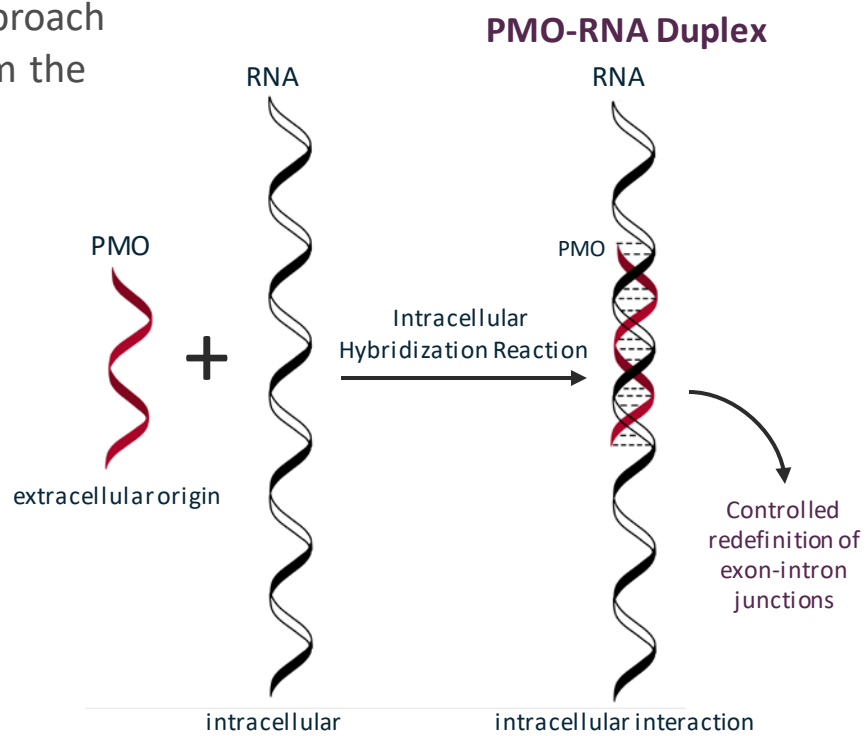
Delivery, delivery, delivery

Cellular uptake by muscle cells has been notoriously challenging for antisense drugs

Skeletal muscle, representing 30%-40% of body mass, has remained one of the most difficult targets—until now

PMO Works by Forming Duplexes With RNA Inside the Cell

- This powerful antisense therapeutic approach works only if PMO can be delivered from the extracellular space into the cell



RNA, ribonucleic acid.

Precision Genetic Drugs Must Be Able to Enter the Cell and Stay There

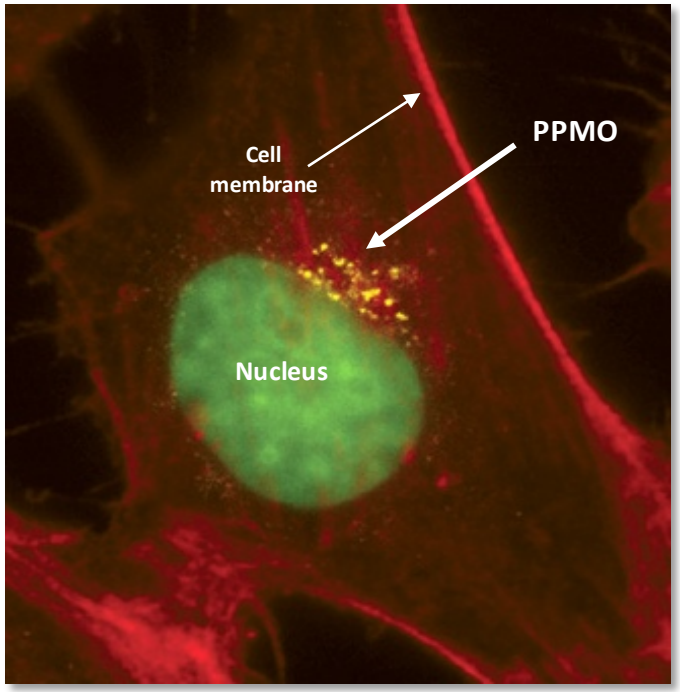
Objective

- To invent new proprietary platforms that enable the safe and efficacious cellular delivery of PMO-based antisense therapeutics

Approach

- Apply the science of cell delivery to design new delivery chemistries based on the classic PMO structure
- A delivery peptide interacts with cellular structures, particularly the cell membrane, to drive the drug into the cell

Crossing the Cell Membrane With PPMO



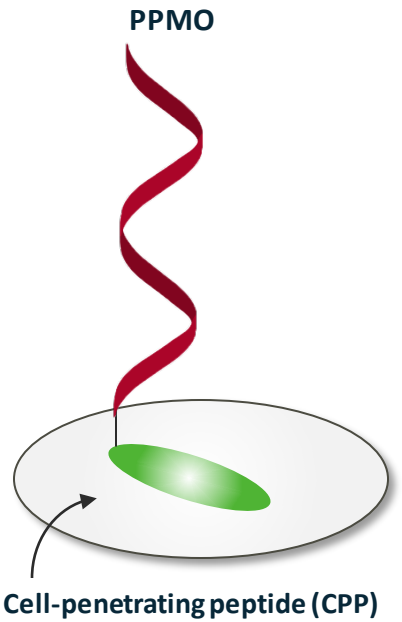
PPMO, peptide-conjugated phosphorodiamidate morpholino oligomer.

PPMO Adds a Delivery Peptide and Opens the Door to Cellular Entry

PPMO = PMO + Delivery Peptide

PMO is compatible with cell-penetrating delivery peptides

- This compatibility is rooted in the PMO's uncharged (nonionic) phosphorodiamidate linkers
  - There is no water solubility problem as observed with phosphorothioates
- The peptide enables delivery of PMO base sequences to their site of action within muscle cell nuclei
- Our proprietary cell-penetrating peptide invention leads to PPMOs with excellent efficacy and safety (based on preclinical data)
- There are 6 PPMOs in the Sarepta clinical pipeline
  - **SRP-5051, SRP-5052, SRP-5053, SRP-5044**, **SRP-5045,** and **SRP-5050**



The Architecture of PPMO; Let's Build a PPMO

- PMO is made first,

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In the beginning, primordial subunits are overlapped and joined at N

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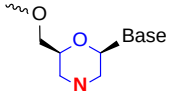

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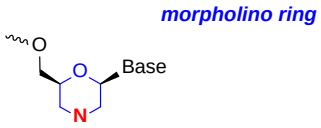

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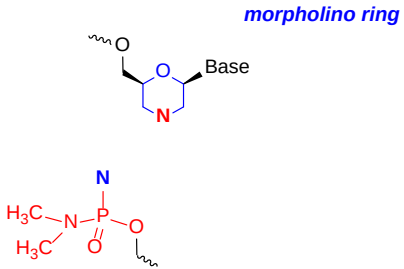

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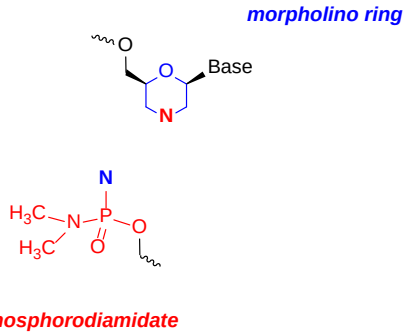

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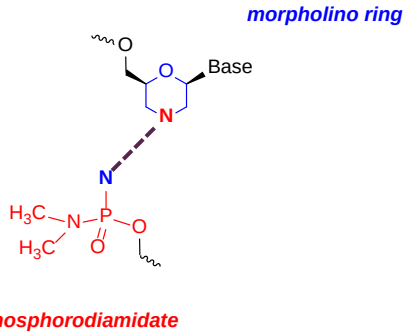

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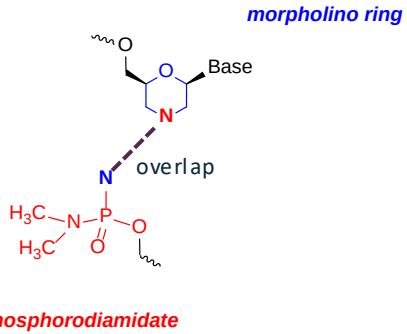

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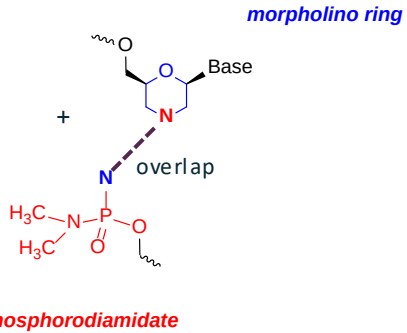

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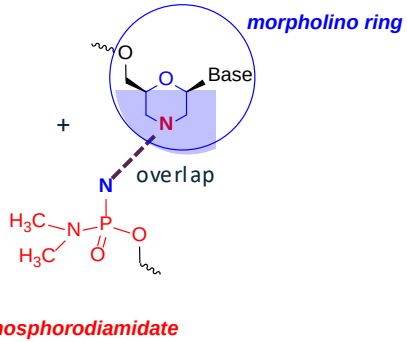

phosphorodiamidate

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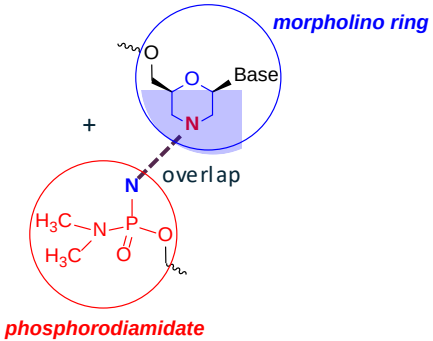

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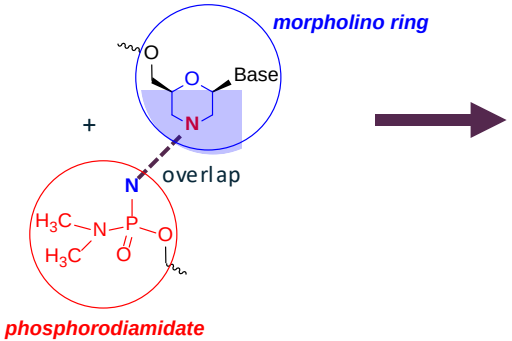

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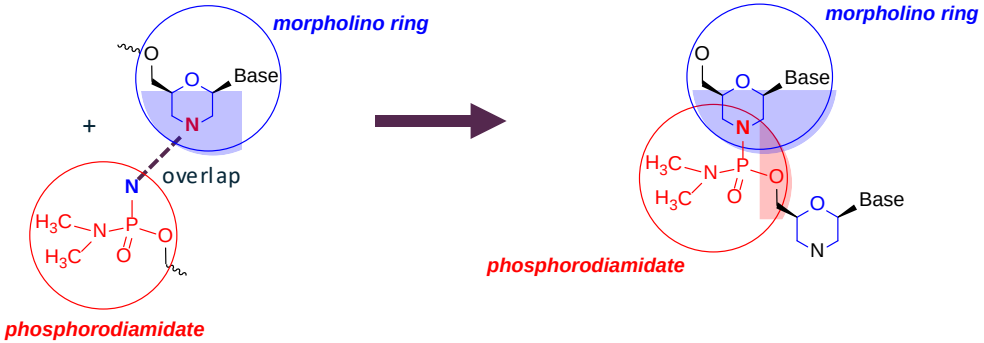

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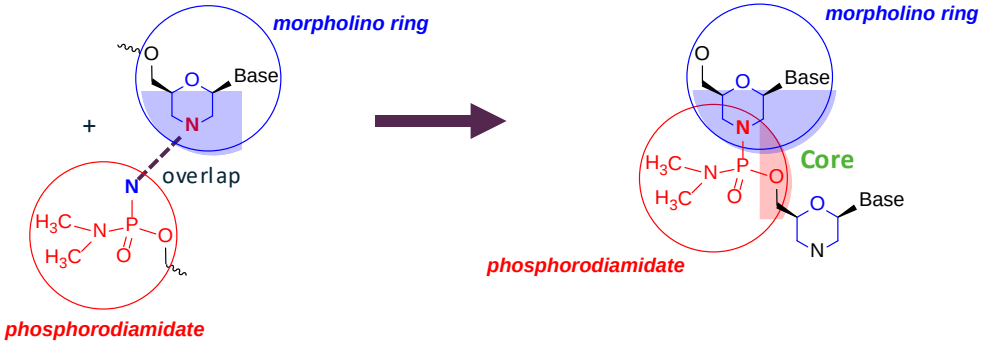

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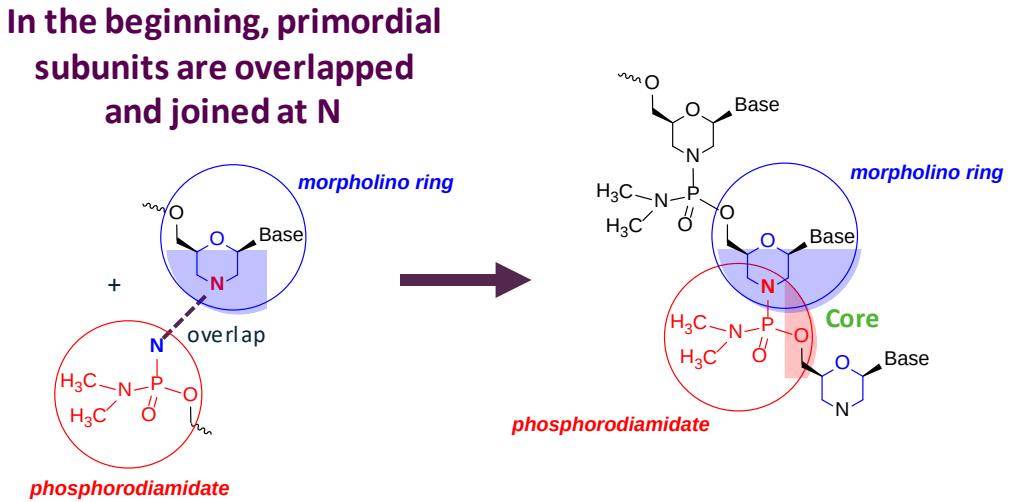

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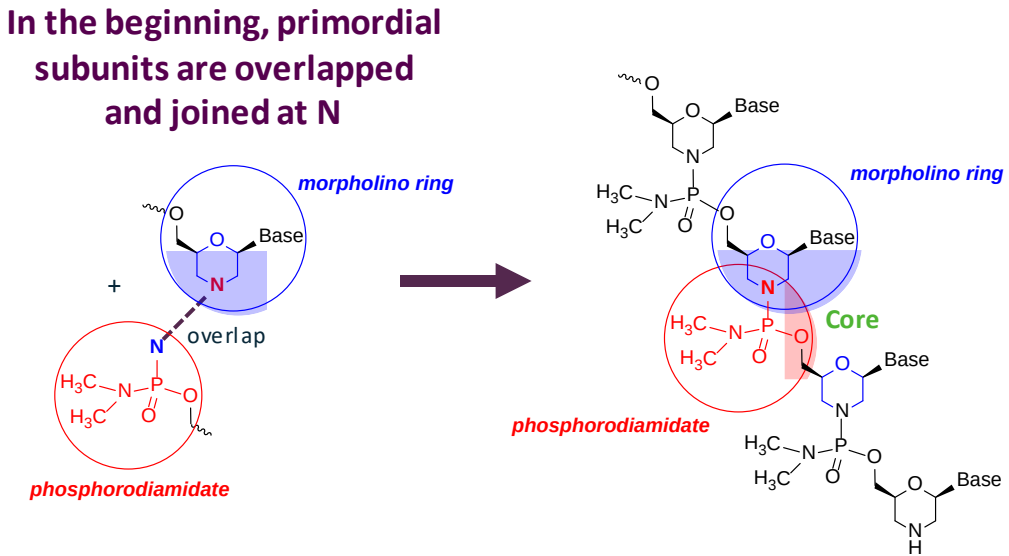

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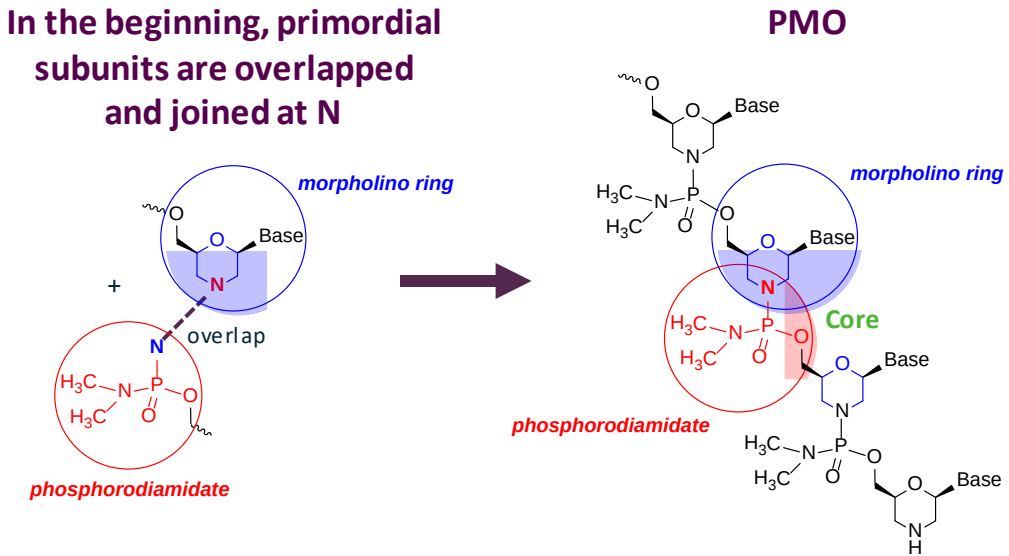

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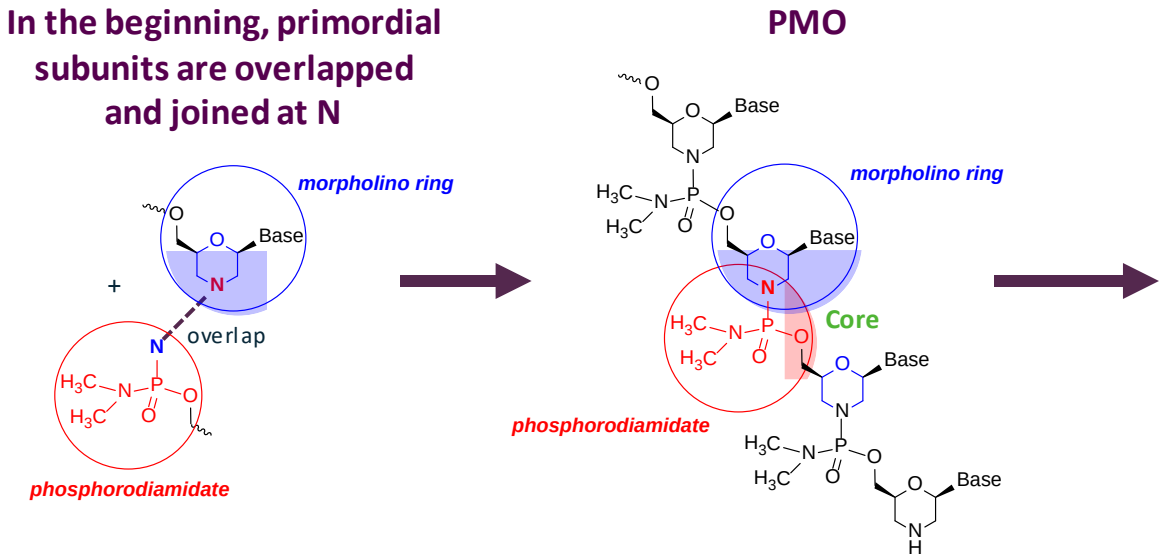
- PMO is made first, and then joined to a CPP



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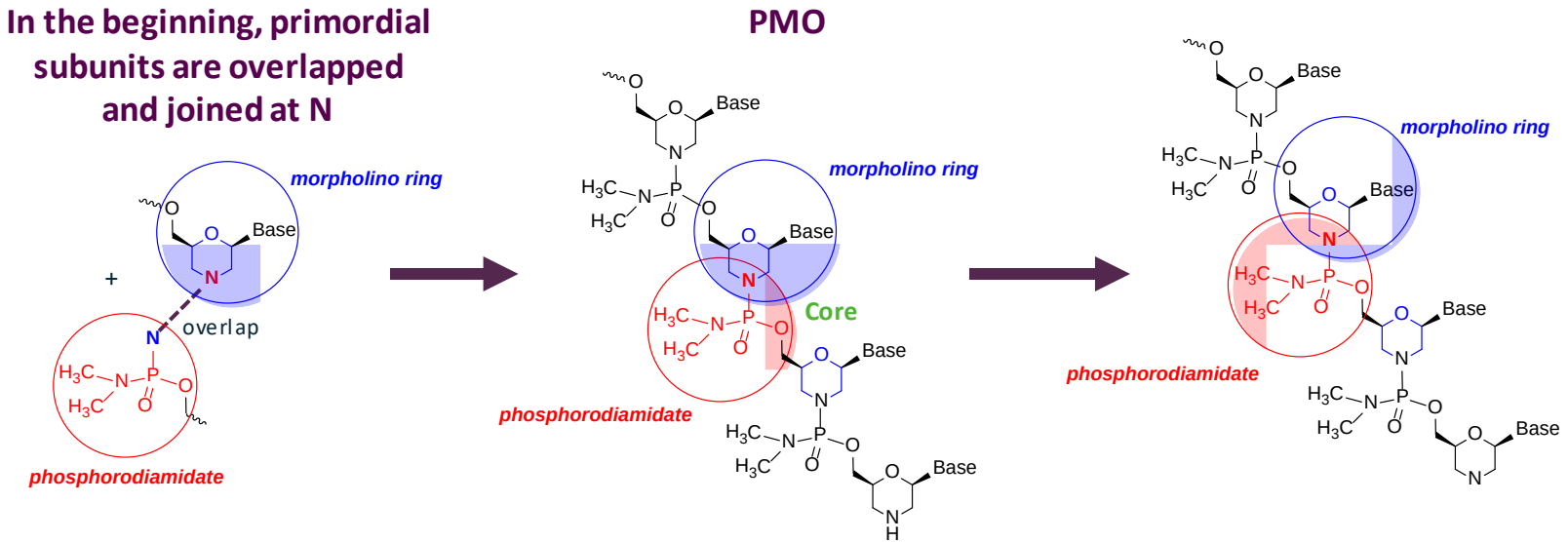

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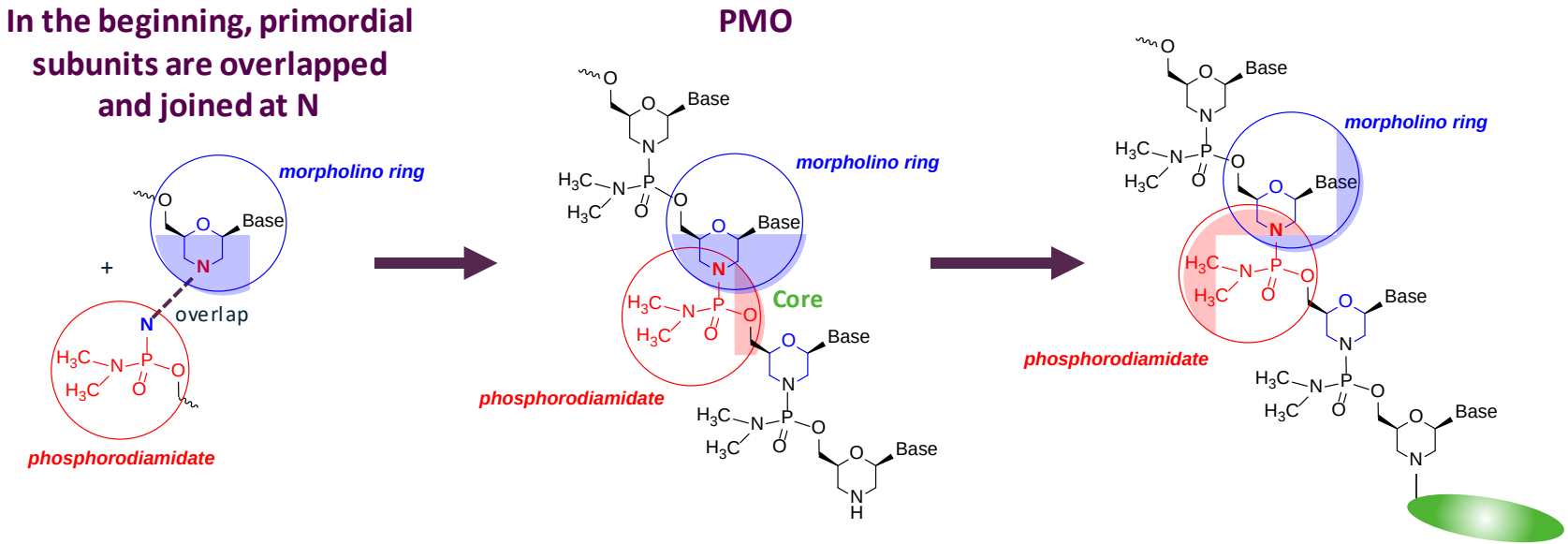

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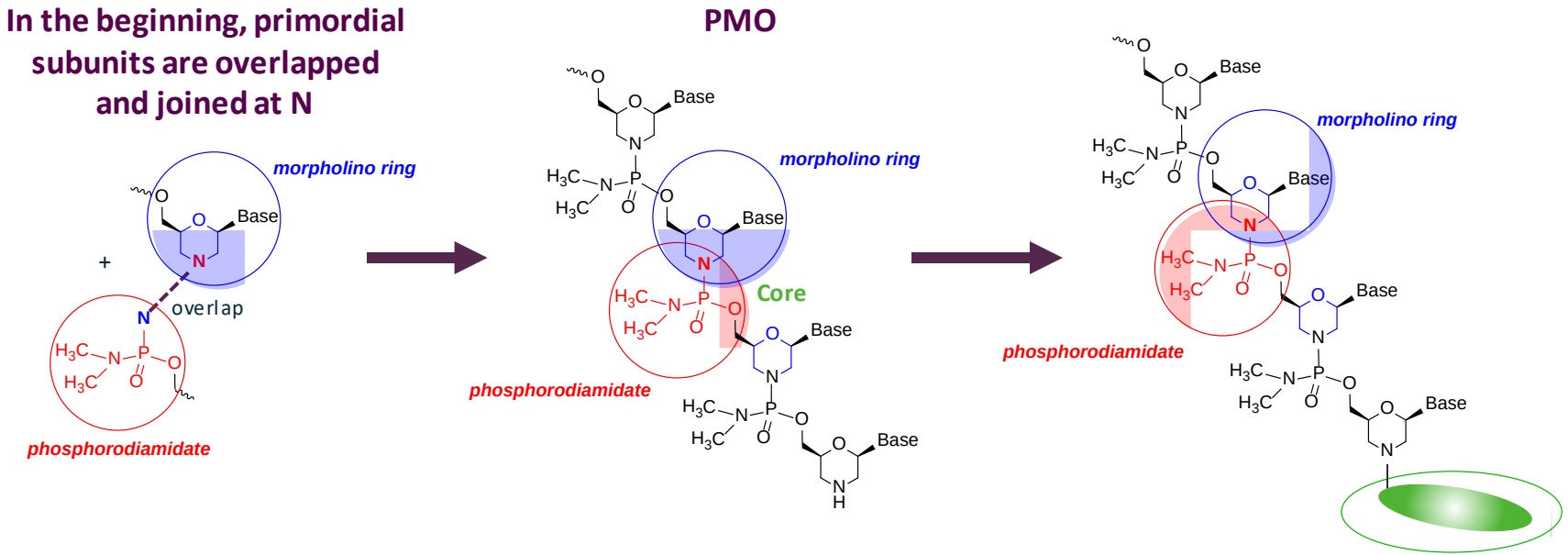

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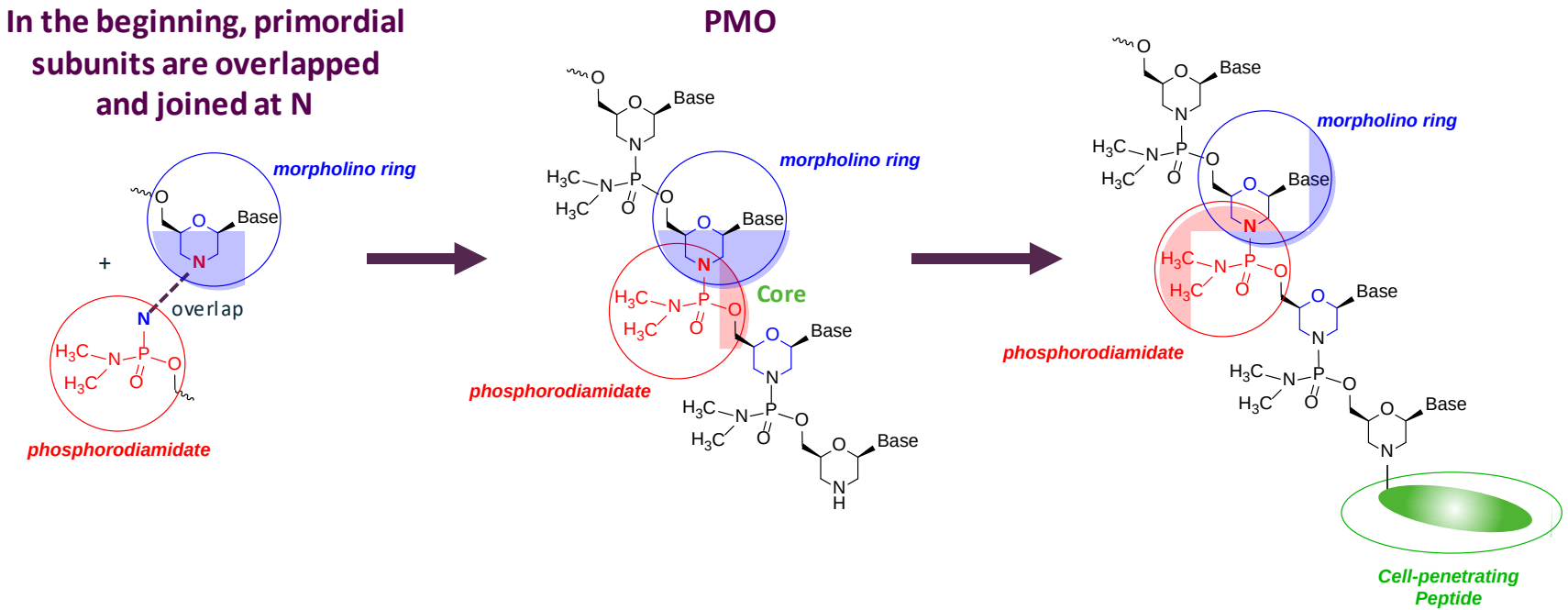

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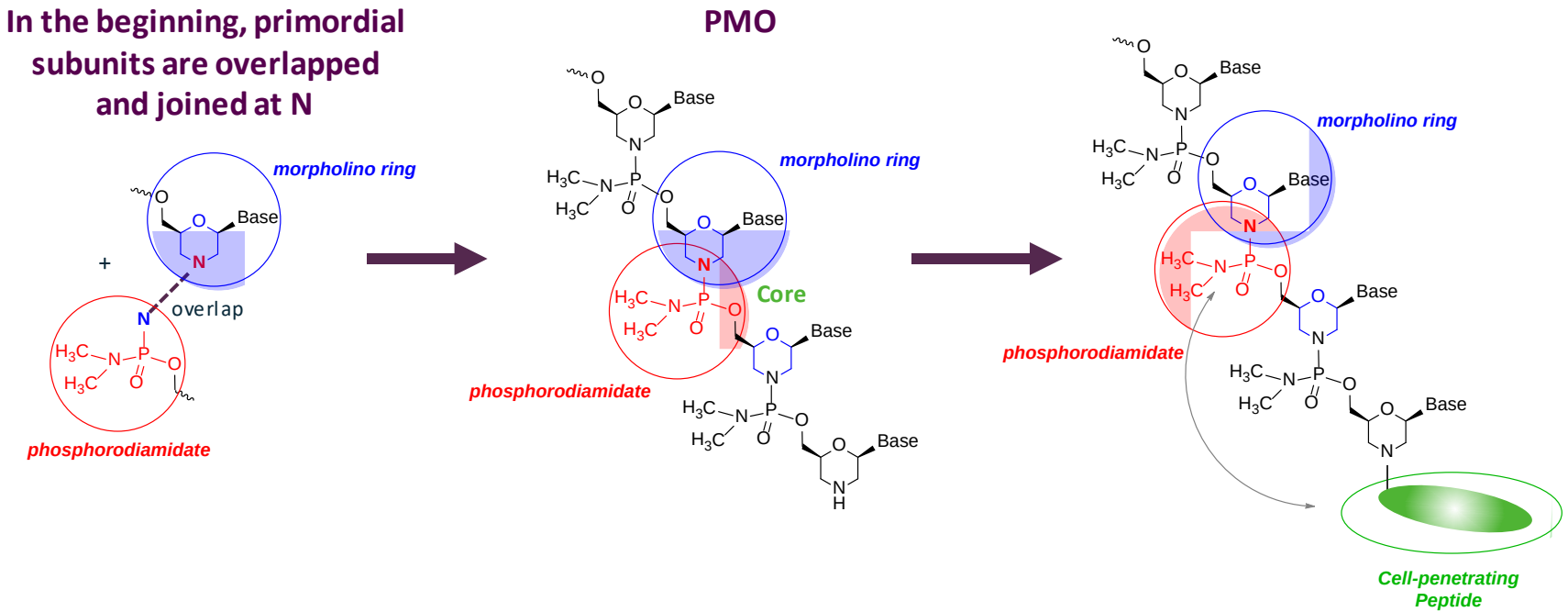

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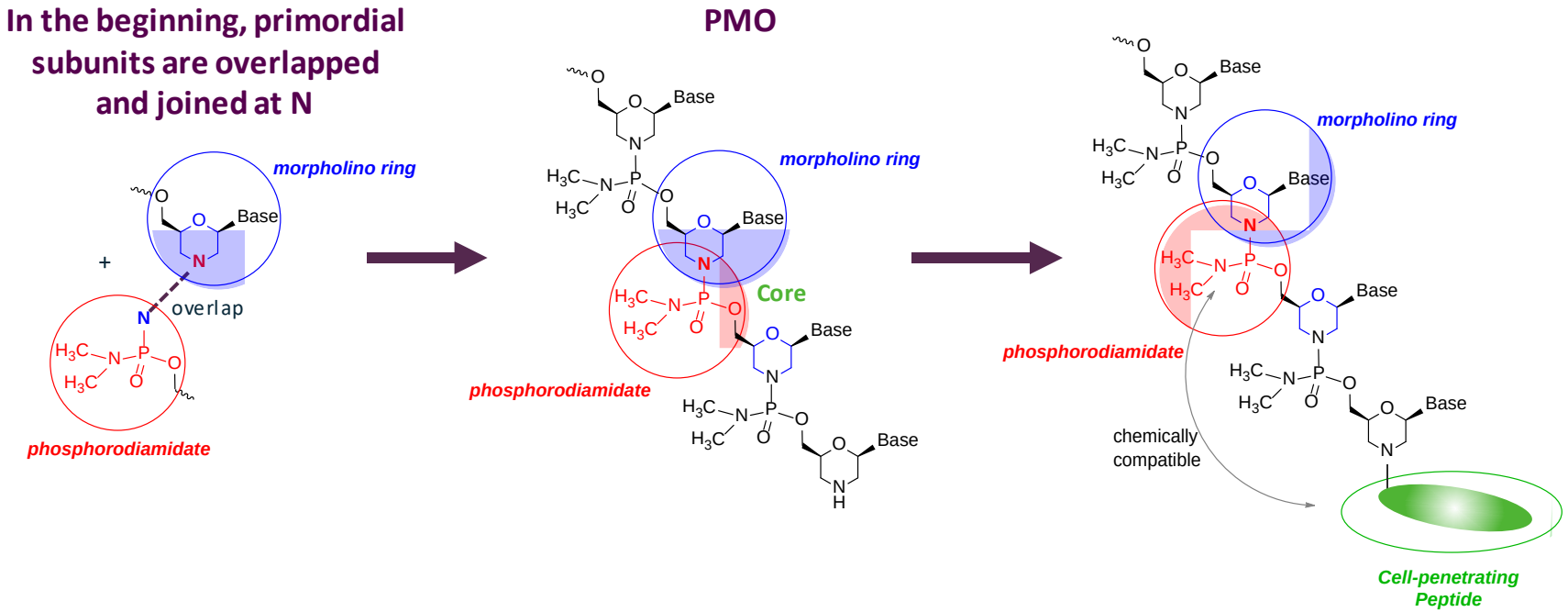

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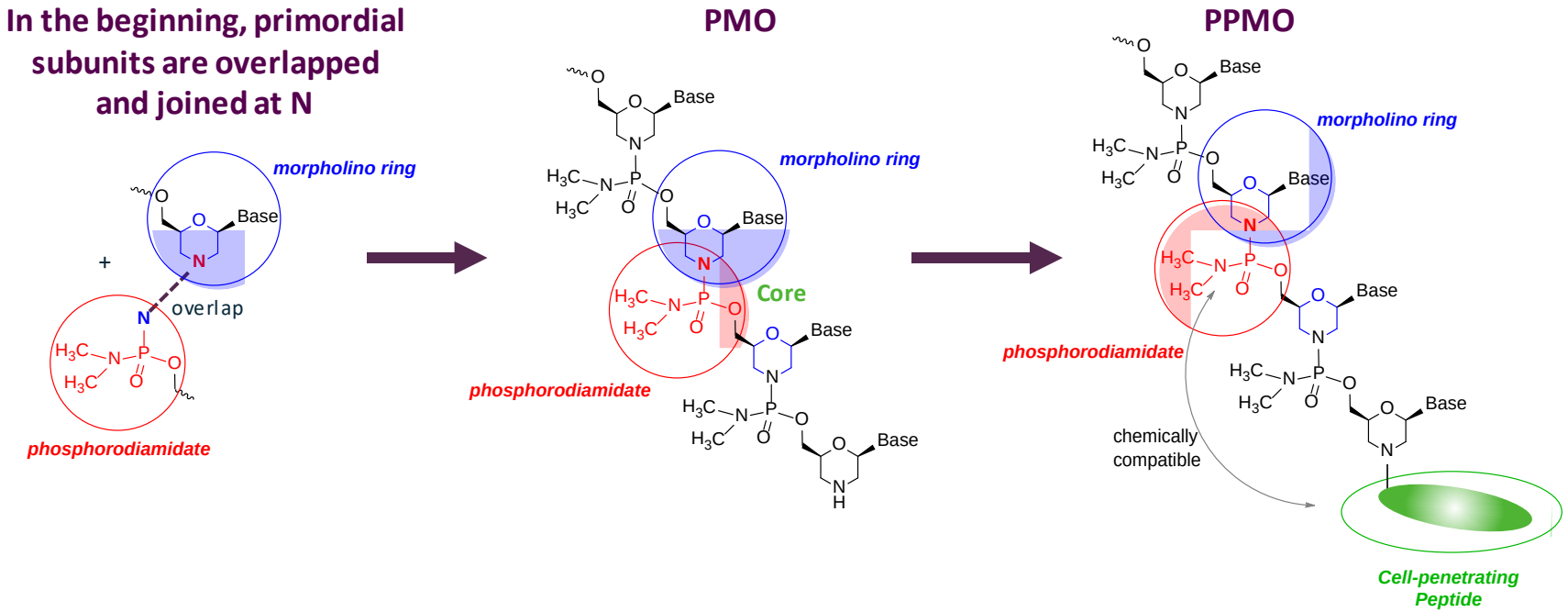
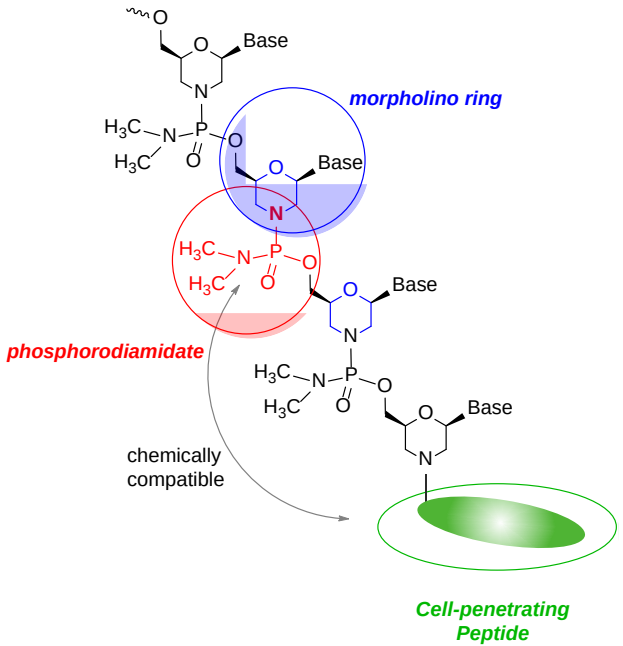
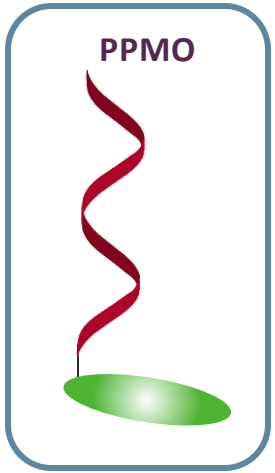


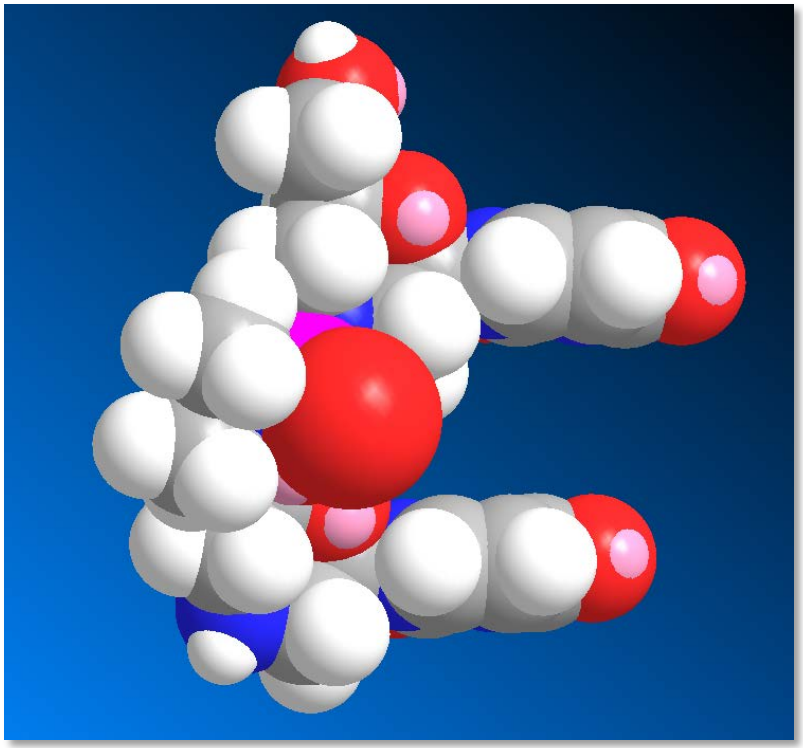
PPMO Is Composed of a PMO and a CPP

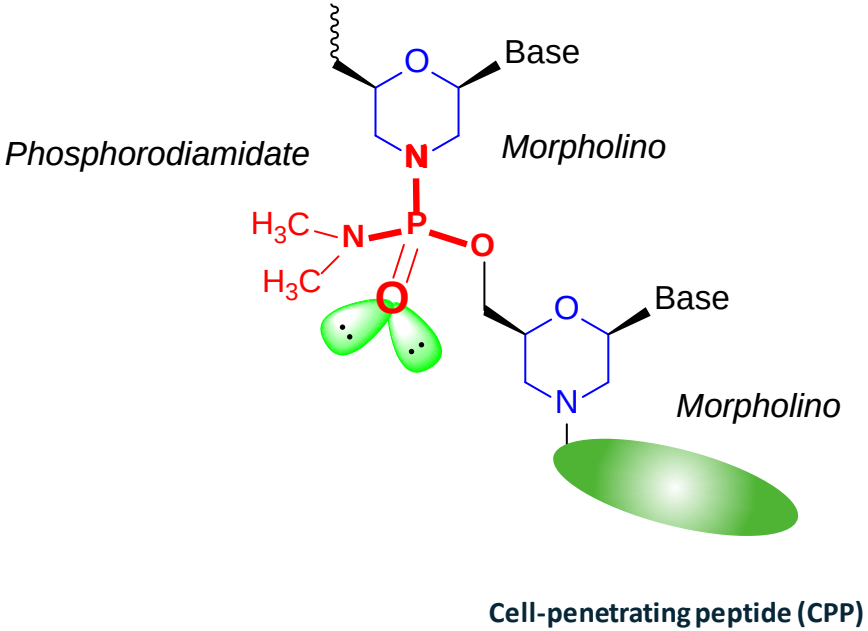
PPMO attributes
• Excellent delivery to muscle cell nuclei to potentially affect exon skipping
• Applicable across many diseases, including those in central nervous system
• Very high water solubility due to peptide and core
• Extreme stability against nucleases
• Excellent hybridization and formation of PMO-RNA duplexes





PPMO Core 3D Structure

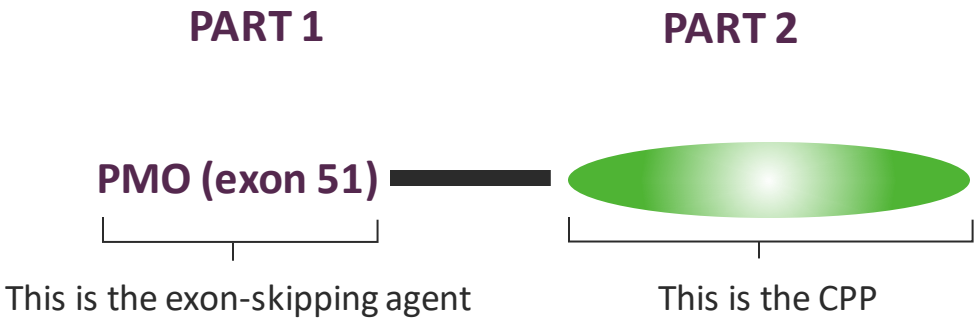




SRP-5051: What Is It?

SRP-5051 is made of 2 parts:

1. a **PMO** containing an exon 51 sequence
2. a cell-penetrating **peptide**



Development of the Proprietary Sarepta CPP

- Our peptide was optimized for a balance of safety and efficacy in concert with PMO

β-peptide, a potent and toxic CPP

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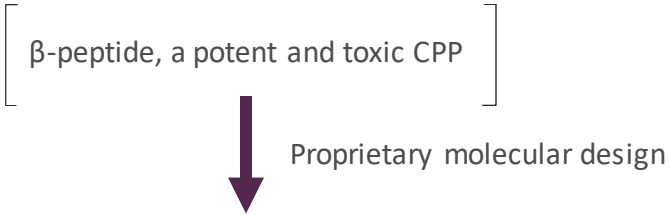

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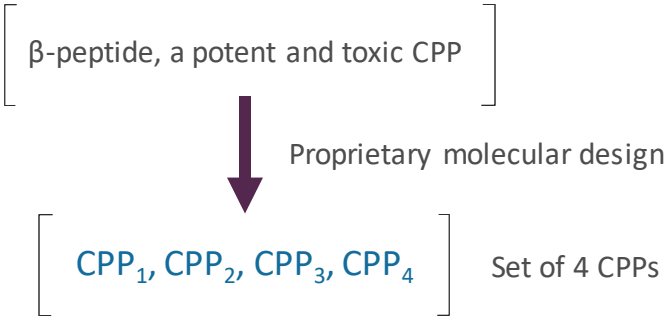

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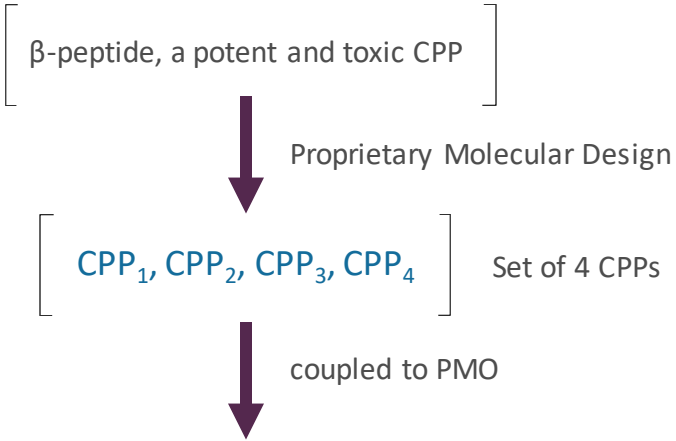

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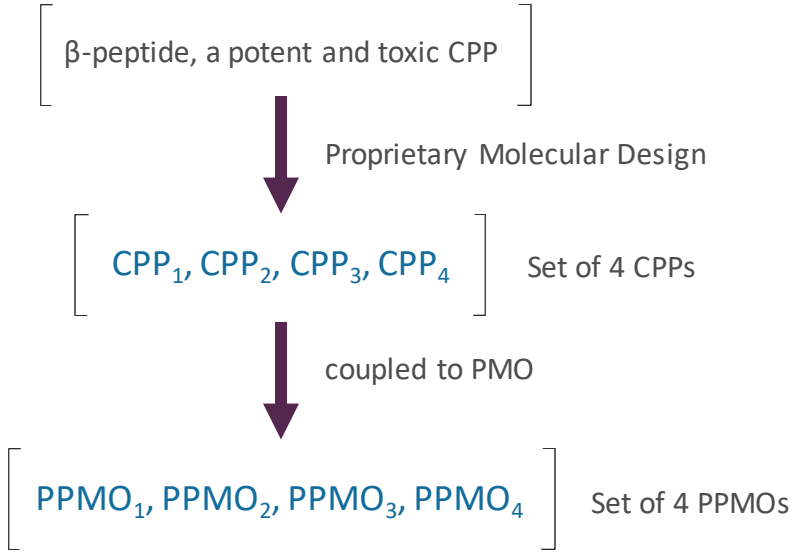

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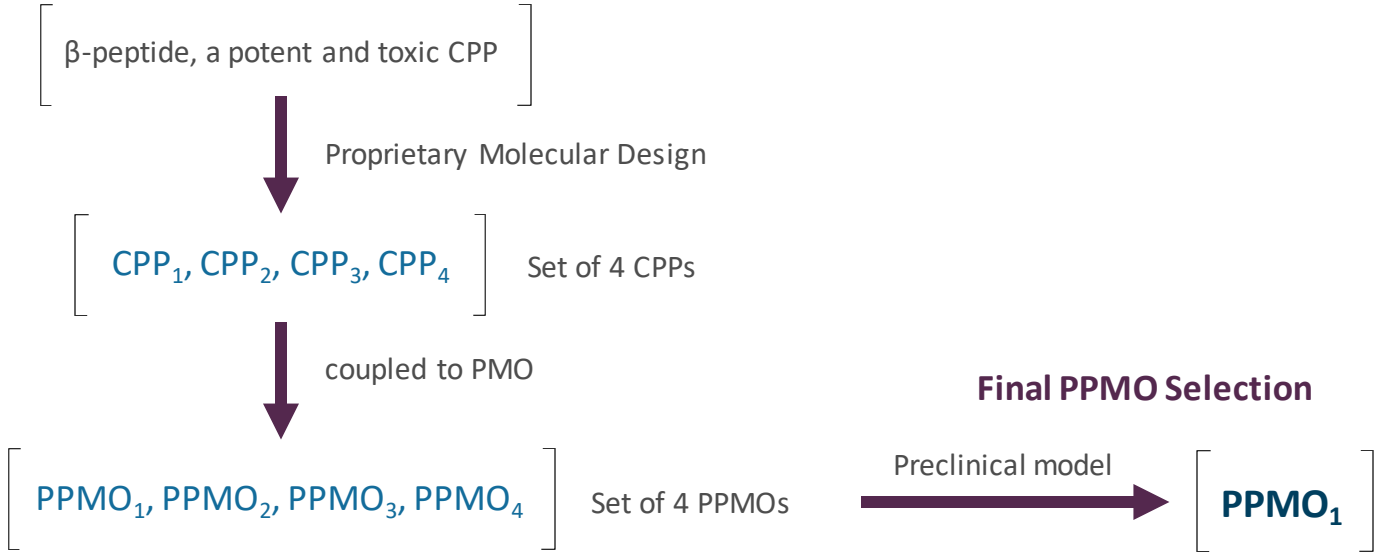
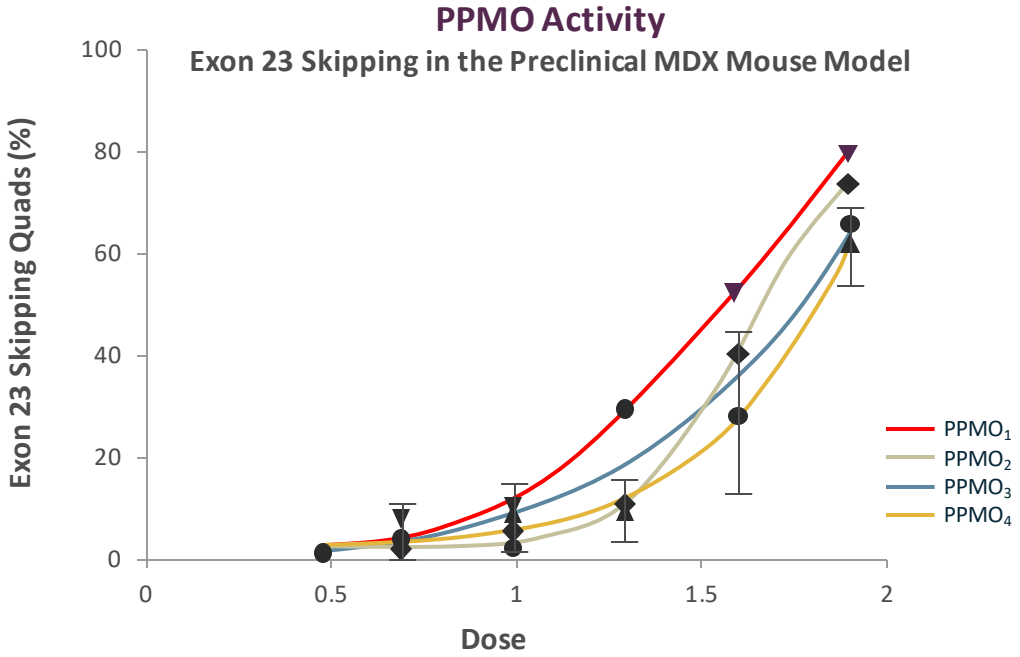


PPMO Works

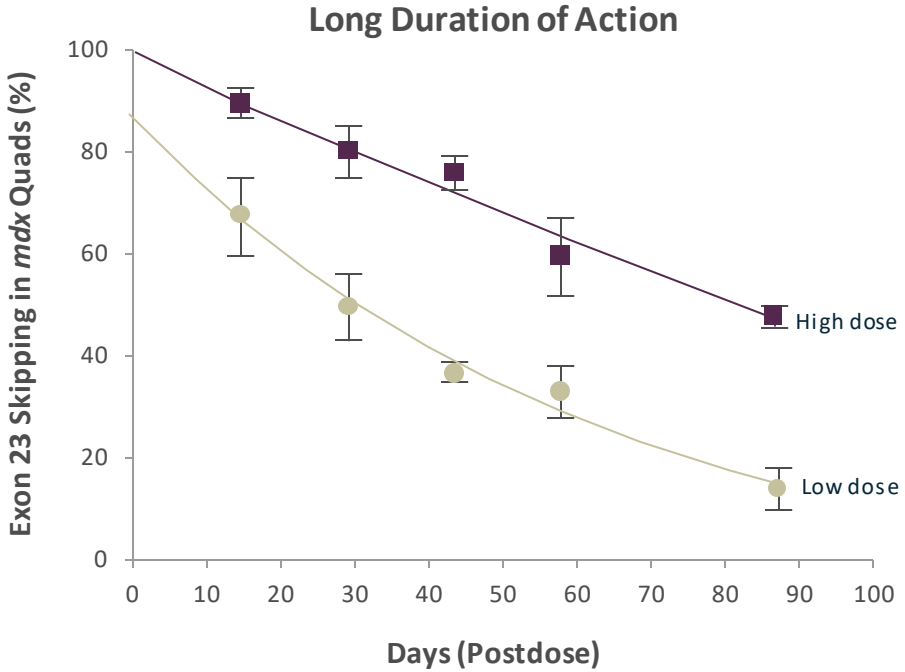
Highly effective exon skipping in our preclinical model after a single IV dose of PPMO



IV, intravenous.

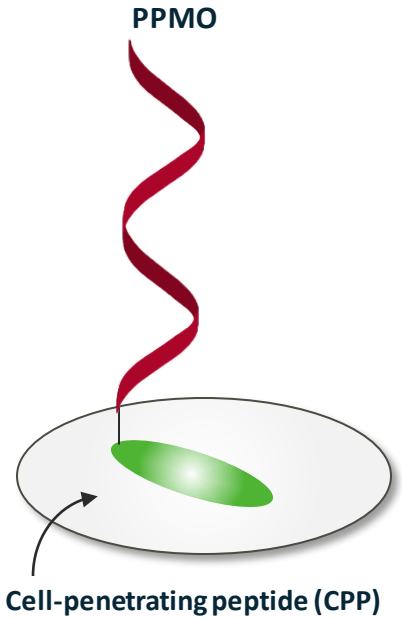
PPMO Shows High Efficiency and Long Duration of Action

Prolonged exon skipping in our preclinical model after a single IV dose of PPMO



Summary

- Peptide conjugation of PMO realizes the therapeutic potential of antisense oligos, especially in rare disease treatment
- The peptide, morpholino ring, and phosphorodiamidate subunits are assembled into a therapeutic engine that is the apex of compatibility
- The well-known safety and antisense activity of PMO is perpetuated and dramatically enhanced by our proprietary CPP



OUR VISION FOR THE FUTURE OF

Precision Genetic Medicine

SAREPTA THERAPEUTICS 2018 R&D DAY

PPMO for Duchenne Muscular Dystrophy

Marco Passini, PhD

Senior Director of Biology

Sarepta Therapeutics, Inc.

Cambridge, MA

PPMO Is Sarepta's Next-generation RNA Platform for DMD

Thesis

Conjugation of a proprietary cell-penetrating peptide (CPP) improves the delivery of PMO to muscle

↓

Results in high levels of exon skipping and dystrophin protein in muscle

↓

Results in potential transformative improvement in muscle function

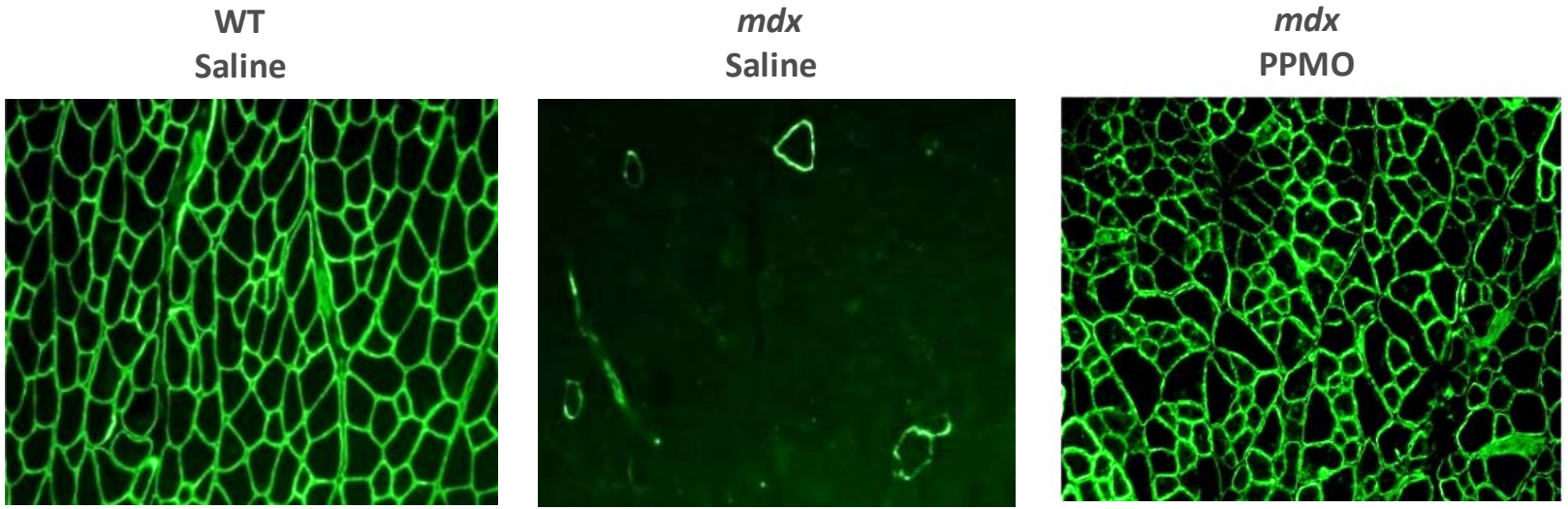
Preclinical Models

Proof-of-concept analysis of PPMO compounds in preclinical models

- M23D-CPP in *mdx* mice
- Eteplirsen-CPP (SRP-5051) in normal NHPs
- Golodirsen-CPP (SRP-5053) in normal NHPs

DMD, Duchenne muscular dystrophy; *mdx*, DMD mouse; NHP, nonhuman primate; PMO, phosphorodiamidate morpholino oligomer; PPMO, peptide-conjugated phosphorodiamidate morpholino oligomer; RNA, ribonucleic acid.

Most Muscle Cells Express Dystrophin Following a Single PPMO Dose in Preclinical Models



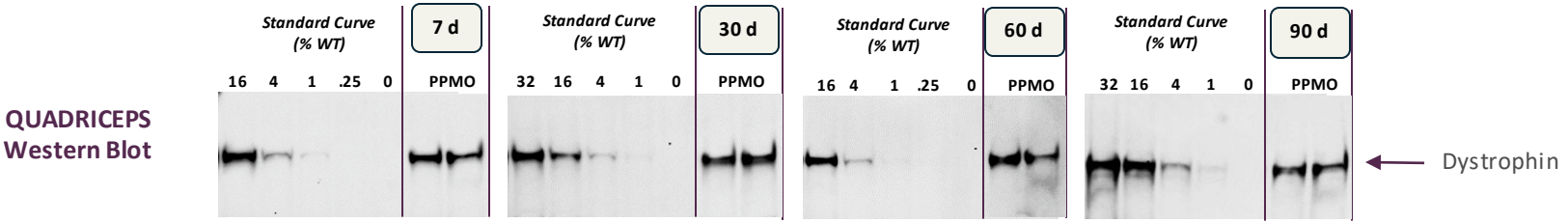
- A single intravenous (IV) dose of PPMO restores dystrophin protein (green) throughout the muscle

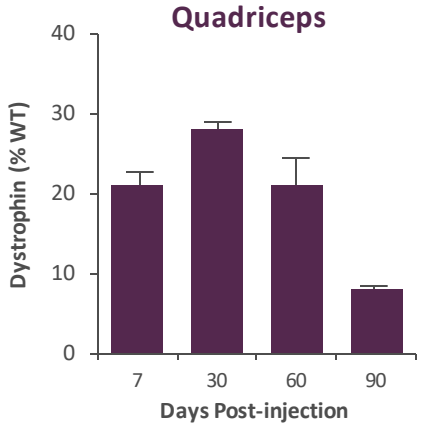
WT, normal mouse.

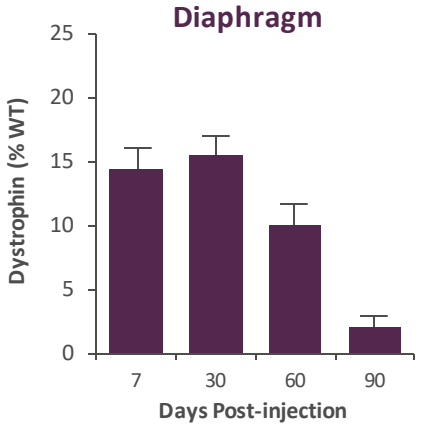
mdx mice were treated with a single IV dose of saline or PPMO at 40 mg/kg, and WT mice were treated with saline.

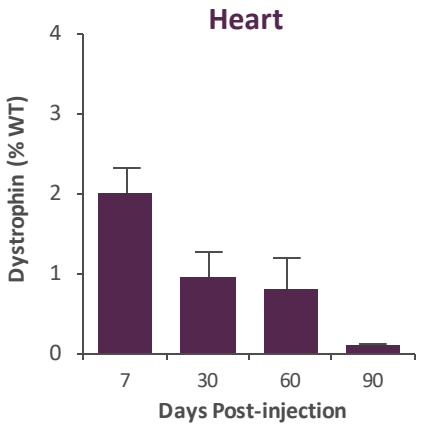
Animals were analyzed at 30 days post-injection by immunohistochemistry to detect dystrophin protein on frozen tissue sections (n=6 per group).

Long Duration of Action:
Dystrophin Is Detected in Muscle 3 Months After a Single Dose of PPMO



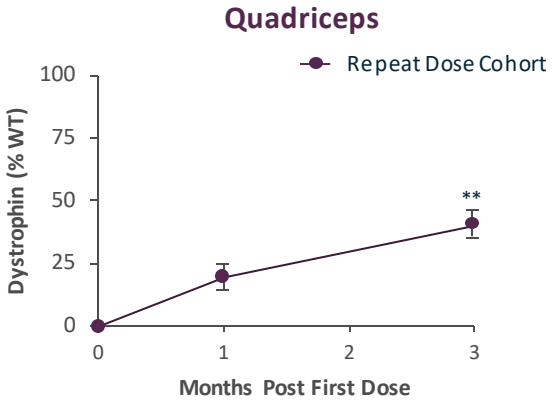


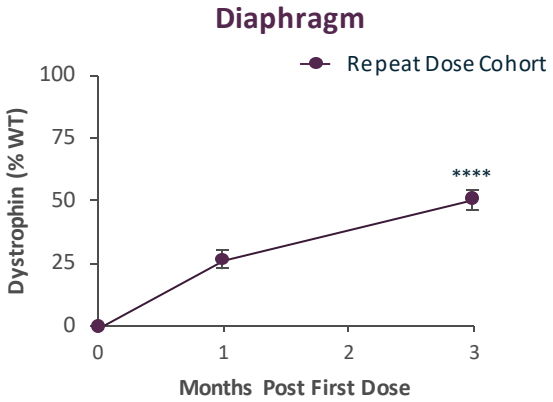


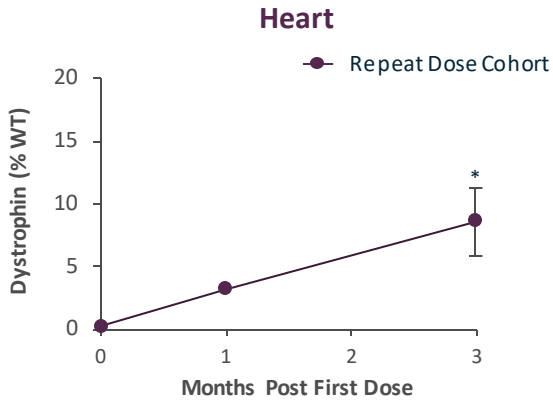


mdx mice were treated with a single IV dose of PPMO at 40 mg/kg and analyzed at 7, 30, 60, or 90 days post-injection (n=6 per time point).

Repeat PPMO Doses Increase and Sustain High Levels of Dystrophin in Muscle





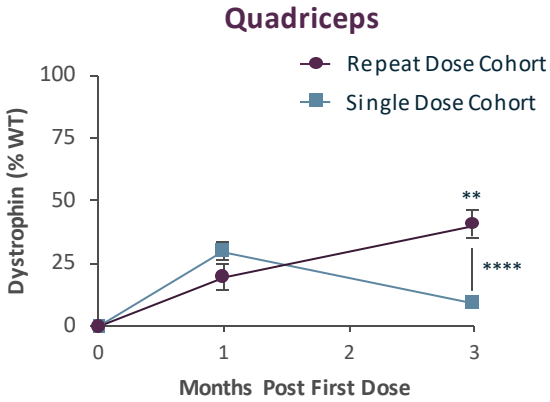


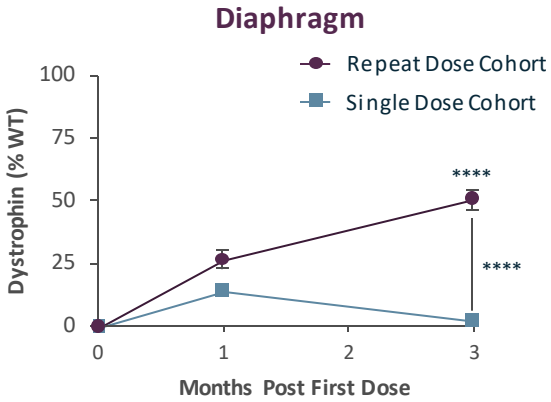
Repeat Dose Cohort (Purple)

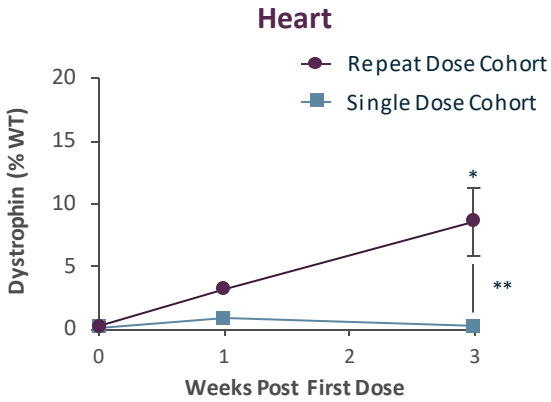
- Group 1: *mdx* mice were treated with a single IV dose of PPMO at 40 mg/kg and analyzed at 1 month (n=6)
- Group 2: *mdx* mice were treated with three monthly IV doses of PPMO at 40 mg/kg and analyzed at 3 months (n=6)

Graphs are mean +/- SE; Statistics were performed using the *One Way Anova Tukey Multiple Comparison* Test (*p<0.05, **p<0.01, ****p<0.0001). The significant values shown are the Repeat Dose Cohort at 3 months (Group 2) versus the Repeat Dose Cohort at 1 month (Group 1); and the Repeat Dose Cohort at 3 months (Group 2) versus the Single Dose Cohort at 3 months (Group 4).

Repeat PPMO Doses Increase and Sustain High Levels of Dystrophin in Muscle







Repeat Dose Cohort (Purple)

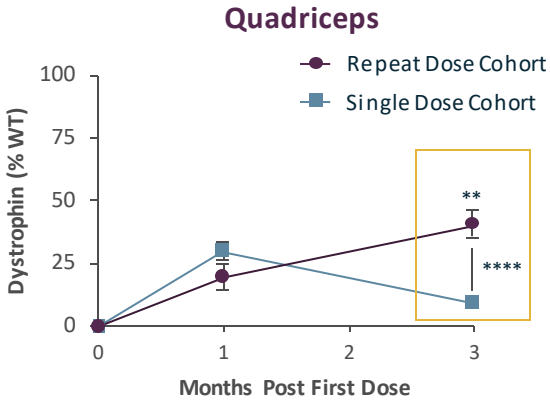
- Group 1: *mdx* (DMD) mice were treated with a single IV dose of PPMO at 40 mg/kg and analyzed at 1 month (n=6)
- Group 2: *mdx* (DMD) mice were treated with three monthly IV doses of PPMO at 40 mg/kg and analyzed at 3 months (n=6)

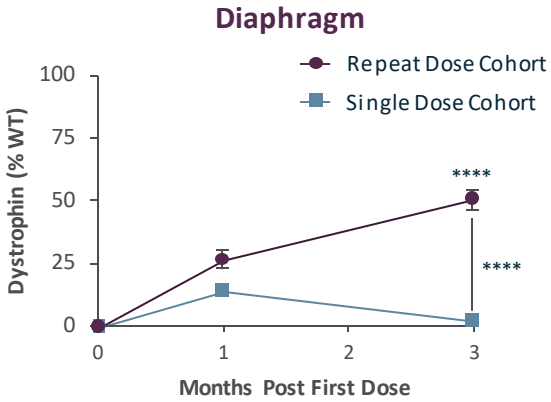
Single Dose Cohort (Blue)

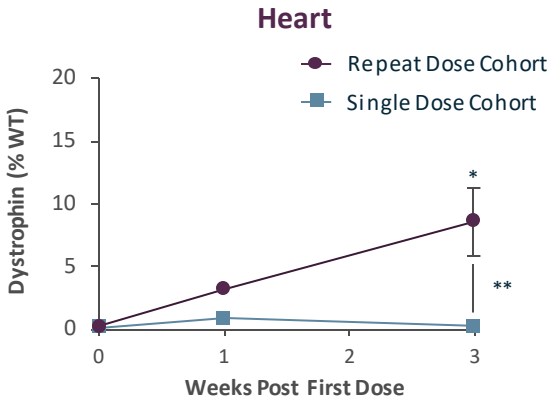
- Group 3: *mdx* (DMD) mice were treated with a single IV dose of PPMO at 40 mg/kg and analyzed at 1 month (n=6)
- Group 4: *mdx* (DMD) mice were treated with a single IV dose of PPMO at 40 mg/kg and analyzed at 3 months (n=6)

Graphs are mean +/- SE; Statistics were performed using the *One Way Anova Tukey Multiple Comparison* Test (*p<0.05, **p<0.01, ****p<0.0001). The significant values shown are the Repeat Dose Cohort at 3 months (Group 2) versus the Repeat Dose Cohort at 1 month (Group 1); and the Repeat Dose Cohort at 3 months (Group 2) versus the Single Dose Cohort at 3 months (Group 4).

Repeat PPMO Doses Increase and Sustain High Levels of Dystrophin in Muscle







Repeat Dose Cohort (Purple)

- Group 1: *mdx* (DMD) mice were treated with a single IV dose of PPMO at 40 mg/kg and analyzed at 1 month (n=6)
- Group 2: *mdx* (DMD) mice were treated with three monthly IV doses of PPMO at 40 mg/kg and analyzed at 3 months (n=6)

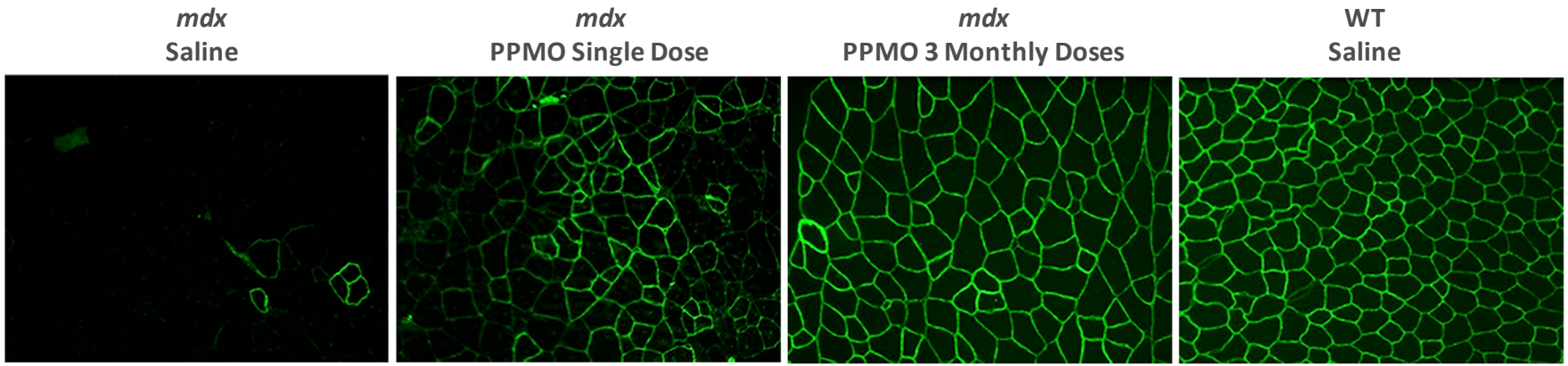
Single Dose Cohort (Blue)

- Group 3: *mdx* (DMD) mice were treated with a single IV dose of PPMO at 40 mg/kg and analyzed at 1 month (n=6)
- Group 4: *mdx* (DMD) mice were treated with a single IV dose of PPMO at 40 mg/kg and analyzed at 3 months (n=6)

Graphs are mean +/- SE; Statistics were performed using the *One Way Anova Tukey Multiple Comparison* Test (*p<0.05, **p<0.01, ****p<0.0001). The significant values shown are the Repeat Dose Cohort at 3 months (Group 2) versus the Repeat Dose Cohort at 1 month (Group 1); and the Repeat Dose Cohort at 3 months (Group 2) versus the Single Dose Cohort at 3 months (Group 4).

Repeat PPMO Dosing Maintains Widespread Dystrophin Expression in Muscle

Dystrophin Expression in the Quadriceps at 3 Months



Dystrophin immunohistochemistry on tissue sections

mdx mice were treated with 3 monthly IV doses of PPMO at 40 mg/kg per dose, or a single IV dose of PPMO at 40 mg/kg (N=6 per time point per group).
Animals were analyzed 3 months after the initial dose by immunohistochemistry to detect dystrophin protein in tissue sections.
Control age-matched *mdx* mice and WT mice treated with saline are also shown.

PPMO Dose-response Study

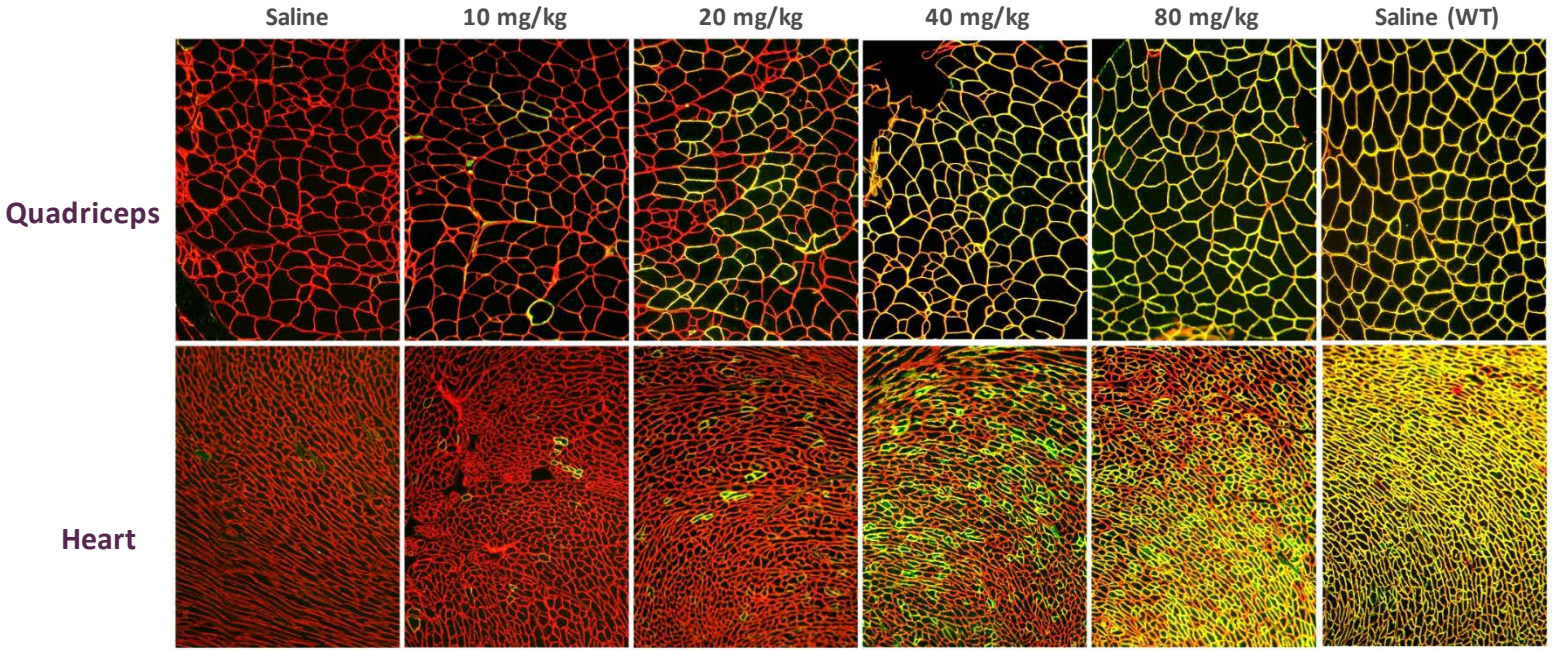
- Goals of the study:
  - Show a dose-response increase in exon skipping and dystrophin protein
  - Show a decrease in cellular markers of inflammation and necrosis
  - Show significant improvements in muscle function

Gr	Strain	Mice (N)	Agent	Dose	HED*	In-life Endpoints
1	WT	10	Saline	0 mg/kg	0 mg/kg	**Treatment and Behavioral Schedule** • Systemic injection in 7-week old mice (n=10 per group) • Rotarod test on 9-week old mice (14 days pi) • Grip Strength test on 10-week old mice (21 days pi) • Harvested tissues in 11-week old mice (30 days pi) **Tissues Harvested** • Quadriceps, Biceps, Diaphragm, Heart **Assays on tissue homogenates** • Western blots, Reverse transcriptase PCR and Real-time PCR
2	*mdx*	10	Saline	0 mg/kg	0 mg/kg	
3	*mdx*	10	PPMO	10 mg/kg	0.8 mg/kg	
4	*mdx*	10	PPMO	20 mg/kg	1.6 mg/kg	
5	*mdx*	10	PPMO	40 mg/kg	3.3 mg/kg	
6	*mdx*	10	PPMO	80 mg/kg	6.5 mg/kg	

HED, human equivalent dose.

*A conventional allometric calculation based on body surface area was used to extrapolate doses between species. The allometric scaling factor between mice and humans is 12.3x.

Dose-dependent Increases in Dystrophin Expression With PPMO in Muscle

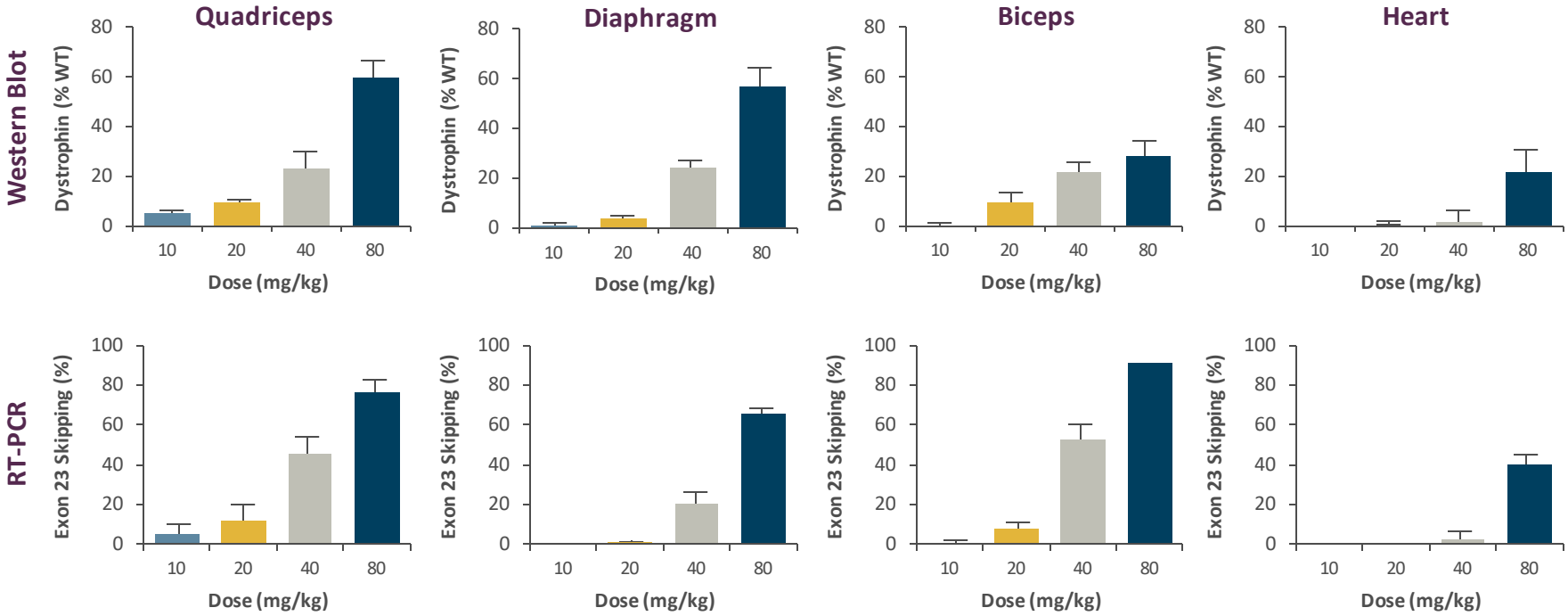


Double immunohistochemistry (Dystrophin/Laminin)

Yellow/orange/green: dystrophin-positive cells; Red: dystrophin-negative cells.

mdx mice at 7 weeks of age were treated with a single IV dose of PPMO at 10, 20, 40, or 80 mg/kg and analyzed at 30 days post-injection (N=4 mice per dose).

PPMO Dose-dependent Increases in Exon Skipping and Dystrophin Levels in Muscle

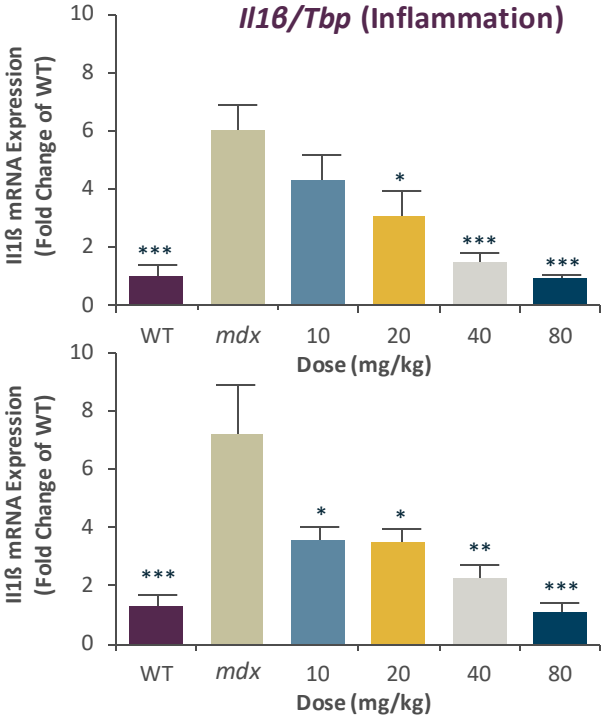


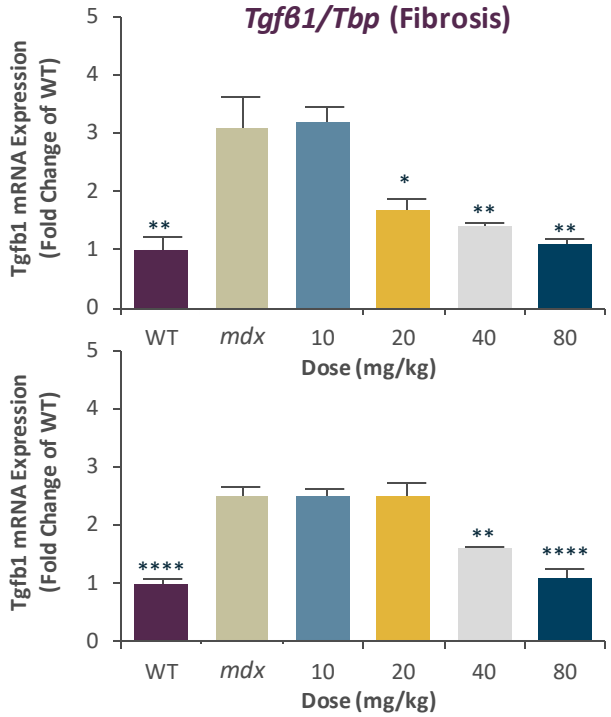
mdx mice at 7 weeks of age were treated with a single IV dose of PPMO at 10, 20, 40, or 80 mg/kg and analyzed at 30 days post-injection (N=6 mice per group).

Dystrophin Restoration Attenuates Markers of Inflammation and Fibrosis in Muscle

Quadriceps

Diaphragm

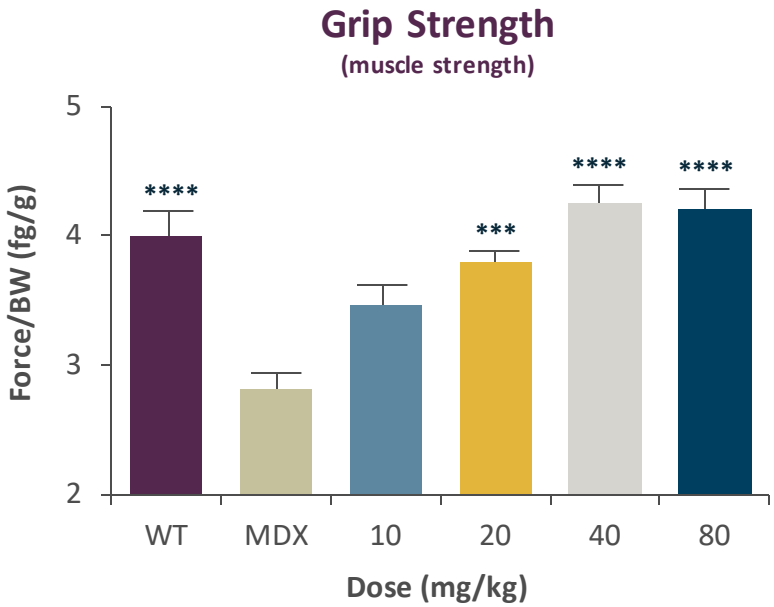


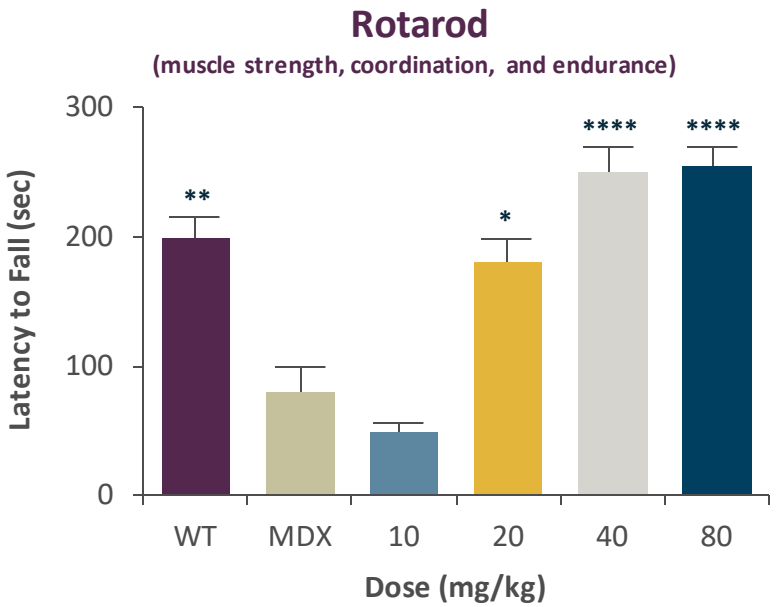


mRNA, messenger RNA; SE, standard error.

mdx mice at 7 weeks were treated with a single IV dose of saline or PPMO at 10, 20,40, or 80 mg/kg, and WT mice at 7 weeks were treated with a single IV dose of saline (n=6 per group). Mice were analyzed for inflammatory (*Il1ß*) and fibrotic (*Tgfß1*) markers by RT-PCR at 30 days post-injection. Graphs are mean ± SE. Statistics were performed using the one-way ANOVA Tukey multiple comparison test, and the significant values shown are vs *mdx* saline (*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001).

PPMO Treatment Improves Muscle Function





mdx mice at 7 weeks of age were treated with a single IV dose of saline or PPMO at 10, 20, 40, or 80 mg/kg, and WT mice at 7 weeks of age were treated with a single IV dose of saline. Mice were tested for grip strength at 10 weeks of age (3 weeks post-injection) and for rotarod at 9 weeks of age (2 weeks post-injection) (n=10 per group). Values shown are mean ± SE. Statistics: One-way ANOVA Tukey multiple comparison test and the significant values shown are vs *mdx* saline (*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001).

Correlation of Dystrophin Levels With Recovery of Muscle Function

	Levels of Dystrophin (% WT) in *mdx* Mice as Measured by Western Blot				
Muscle	**Saline**	**PPMO 10 mg/kg**	**PPMO 20 mg/kg**	**PPMO 40 mg/kg**	**PPMO 80 mg/kg**
Biceps	0	0.3	9.7	20.6	37.1
Quadriceps	0	4.5	10.0	23.7	58.8
Muscle Function Test	**Saline**	**PPMO 10 mg/kg**	**PPMO 20 mg/kg**	**PPMO 40 mg/kg**	**PPMO 80 mg/kg**
Grip Strength	No Improvement	Measurable Improvement	Significant Improvement	Normalization	Normalization
Rotarod	No Improvement	No Improvement	Significant Improvement	Normalization	Normalization

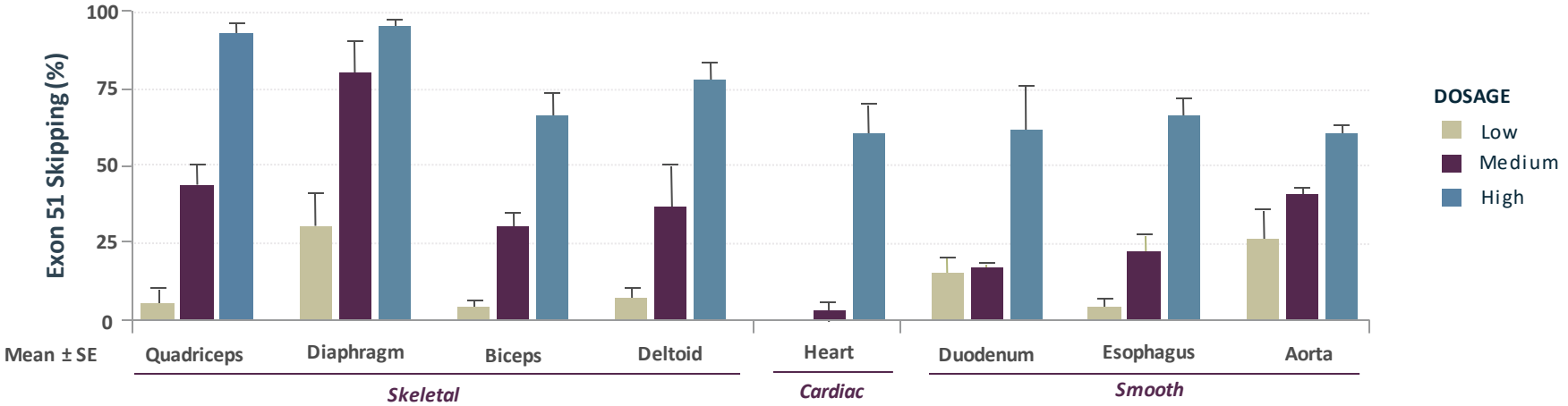
- As low as 0.3% dystrophin expression resulted in a measurable improvement in muscle function (grip strength)
- 10% dystrophin expression produced significant improvements in muscle function
- >20% dystrophin expression normalized muscle function

Correlation of Exon-skipping Levels With Recovery of Muscle Function

	Levels of Exon 23 Skipping in *mdx* Mice as Measured by RT-PCR				
Muscle	**Saline**	**PPMO 10 mg/kg**	**PPMO 20 mg/kg**	**PPMO 40 mg/kg**	**PPMO 80 mg/kg**
Biceps	0	0.6	9.5	54.3	94.0
Quadriceps	0	6.1	14.0	48.2	79.4
Muscle Function Test	**Saline**	**PPMO 10 mg/kg**	**PPMO 20 mg/kg**	**PPMO 40 mg/kg**	**PPMO 80 mg/kg**
Grip Strength	No Improvement	Measurable Improvement	Significant Improvement	Normalization	Normalization
Rotarod	No Improvement	No Improvement	Significant Improvement	Normalization	Normalization

- As low as 0.6% exon skipping resulted in a measurable improvement in muscle function (grip strength)
- >10% exon skipping produced significant improvements in muscle function
- 50% exon skipping normalized muscle function

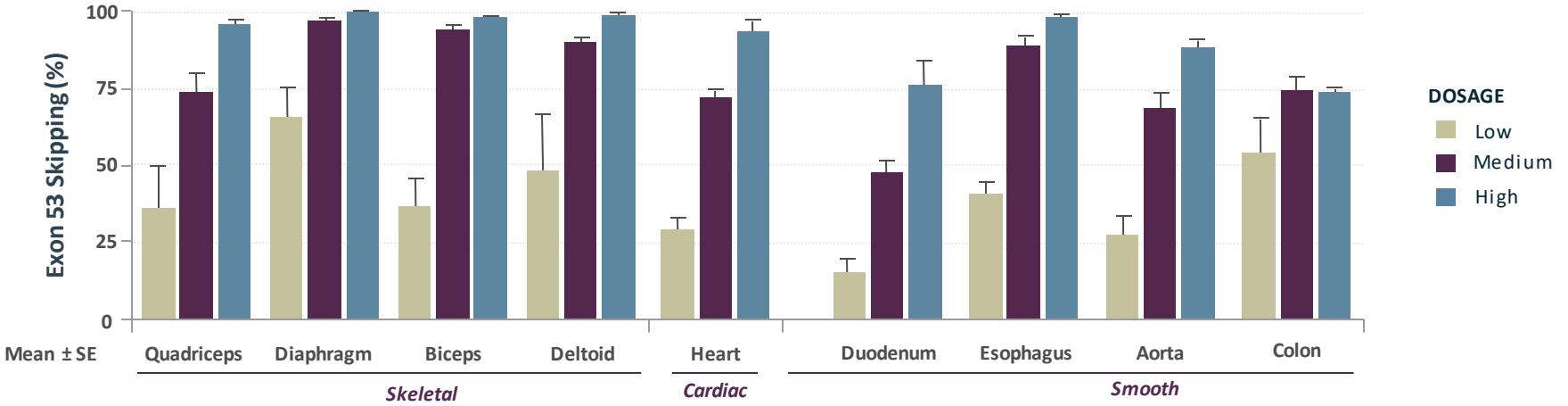
Global Delivery of SRP-5051 (PPMO) to All Relevant Muscle Groups in NHPs



- SRP-5051 = eteplirsen + the CPP used in the *mdx* mouse studies
- Widespread and high levels of exon skipping were observed in muscles that are highly affected in DMD, including >90% exon skipping in quadriceps and diaphragm and >60% in heart and smooth muscles
- Levels of exon skipping that correlated with significant improvements in muscle function in *mdx* mice

Internally generated NHP data.

Global Delivery of SRP-5053 (PPMO) to All Relevant Muscle Groups in NHPs



- SRP-5053 = golodirsen + the CPP used in the *mdx* mouse studies
- Exon skipping was observed in muscles that are highly affected in DMD, including >10% in all analyzed tissues of the low-dose group
- The mid-dose group produced exon-skipping levels that correlated with the normalization of muscle function in *mdx* mice
- The high-dose group produced >90% exon skipping in all analyzed skeletal muscles and in the heart, and >70% in smooth muscles
- Levels of exon skipping that correlated with significant improvements in muscle function in *mdx* mice

Internally generated NHP data.

Summary: PPMO Is a Highly Potent RNA Platform for DMD

Long Lasting Robust Therapeutic Effect in Pre-Clinical Models

- PPMO with our proprietary cell penetrating peptide (CPP) produces high levels of dystrophin in *mdx* mice
  - Therapeutic effect of a single dose of PPMO persists for at least 90 days
  - PPMO treatment decreases inflammatory & fibrotic markers and increases muscle function
- SRP-5051 and SRP-5053 achieves robust exon skipping in skeletal, cardiac and smooth muscles in NHPs
  - Human compounds contain the same proprietary CPP used in the *mdx* mouse studies
  - The levels of exon skipping in NHPs correlates with recovery of muscle function in *mdx* mice
  - SRP-5053 was approximately 2-4 fold more potent than SRP-5051 in NHPs
- PPMO in clinic development
  - Phase 1 clinical trial for SRP-5051 has been initiated (clinicaltrials.gov: NCT03375255)
  - IND filing for SRP-5053 scheduled for Q4 2018
  - Follow-on PPMO compounds scheduled for IND filing in 2019

IND, investigational new drug.

Q&A Session

SAREPTA THERAPEUTICS

OUR VISION FOR THE FUTURE OF

Precision Genetic Medicine

SAREPTA THERAPEUTICS 2018 R&D DAY

Closing Remarks

Doug Ingram
President & Chief Executive Officer
Sarepta Therapeutics, Inc.
Cambridge, MA

Thank You

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