ARCUS-Mediated Excision of Exons 45-55 of the Human Dystrophin Gene using PBGENE-DMD Leads to Durable Muscle Function Improvements In Vivo as a Result of Functional Dystrophin Protein Restoration for the Treatment of Duchenne Muscular Dystrophy

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PBGENE-DMD is Designed to Provide Durable Functional Muscle Improvement for the Majority of Patients with Duchenne Muscular Dystrophy

PERMANENT GENE CORRECTON

PBGENE-DMD designed to provide permanent editing within the dystrophin gene

EVIDENCE SUPPORTING INCREASING FUNCTIONAL IMPROVEMENT

PBGENE-DMD preclinical data shows increased functional improvement over time in skeletal muscle over the course of 9 months

NATURALLY-EXPRESSED DYSTROPHIN PROTEIN

PBGENE-DMD designed to naturally produce dystrophin with known functionality in humans

SATELLITE CELL EDITING FOR DURABLE BENEFIT

PBGENE-DMD has demonstrated satellite cell editing, providing potential for durable benefit over time

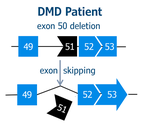
ONE TIME, BROADLY APPLICABLE THERAPY

PBGENE-DMD applicable to up to 60% of patients with DMD with one-time therapy[1]

DMD Therapeutic Landscape

Current Therapeutics Have Limitations and Do Not Provide Durable or Significant Functional Improvements For Patients with DMD

Exon Skipper Therapies



- Lifetime therapy with short-lived effects and limited patient applicability
- Provides low dystrophin protein expression, limiting efficacy[2]
- Safety concerns including hypersensitivity reactions and renal toxicity[3]

Microdystrophin Gene Therapies

- Produce a synthetic protein that is missing a majority of functional domains
- Recently approved synthetic microdystrophin has not been proven to result in significant functional improvement in clinical studies[4]
- Lack of durable effect as the synthetic microdystrophin can be diluted or silenced as myofibers turn over or grow[5]
- Safety concerns with heart/liver toxicities and risk of immune mediated myositis[6]

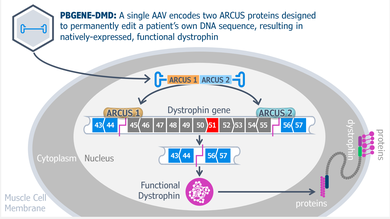
Differentiated Therapeutic Approach that Permanently Corrects the Root Cause of DMD

PBGENE-DMD's Novel Mechanism Results in Gene Correction and Naturally-Produced Functional Dystrophin Protein

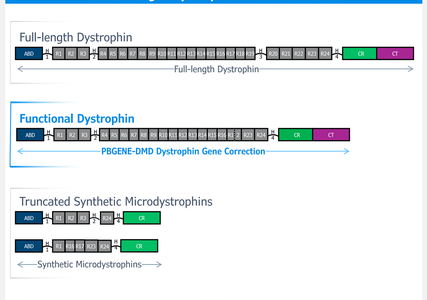
Permanently Correcting the Root Cause
By removing a frequently-mutated region of the dystrophin gene, PBGENE-DMD corrects the reading frame at the DNA level

Naturally-Produced Functional Dystrophin Protein
PBGENE-DMD enables naturally-produced functional dystrophin closely resembling normal dystrophin

Durable Functional Muscle Improvement
PBGENE-DMD has been shown to significantly improve muscle function over time while also editing muscle satellite cells for durable therapeutic benefit



PBGENE-DMD Dystrophin Gene Correction Results in a Functional Dystrophin Retaining the Vast Majority of Full-length Dystrophin Protein Domains

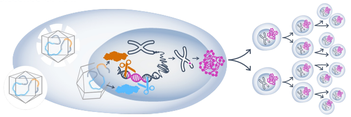


PBGENE-DMD functional dystrophin is present in a subset of Becker patients with mild to asymptomatic phenotypes[7]

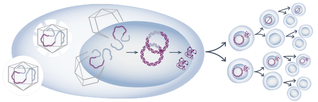
It is expected that as little as 5% expression of the functional dystrophin protein is needed to provide therapeutic benefit[8]

PBGENE-DMD Enables Durable Functional Improvements in Muscle Function Independent of the Persistence of AAV

PBGENE-DMD gene correction results in functional dystrophin protein expression by the human genome, preventing the need for persistence of AAV



Microdystrophin gene therapies deliver a synthetic microdystrophin protein that is expressed from the AAV genome, requiring presence and expression of AAV vector



Durable Improvements in Muscle Function with PBGENE-DMD Treatment

Study Design

Group	Mouse Model	N
PBGENE-DMD ($3x10^{13}$ VG/kg)	Disease	10
PBGENE-DMD ($1x10^{14}$ VG/kg)	Disease	10
Untreated	Disease	10
Untreated	Healthy	10

Mice dosed at 3 weeks of age (equivalent to target patient population of 4-7 years old)
Disease mice are hDMDdel52/mdx, humanized DMD mouse model
All functional readouts were conducted in vivo through Myologica

Key Readouts:

- Satellite Cell Imaging (ISH)
- Dystrophin Protein Restoration (WES)
- Dystrophin Positive Fibers (IF)
- Muscle Force Output

Editing Satellite Cells is Essential for Permanent Effect

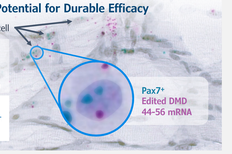
In DMD where myofiber degeneration is continuous, editing satellite cells is essential for permanent therapeutic effect

Satellite cells are the resident stem cells in skeletal muscle and essential for muscle regeneration

Myocytes

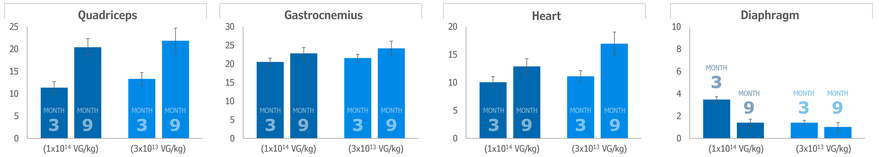
Myofiber

PBGENE-DMD Dystrophin Gene Correction Edits Muscle Satellite Stem Cells, Providing Potential for Durable Efficacy



PBGENE-DMD Restores Functional Dystrophin Protein Across Key Target Muscles

Dystrophin Restoration (%) in Treated Disease Mice

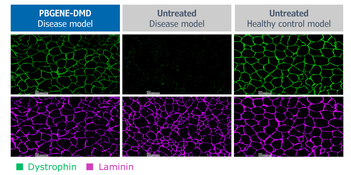


Achieved therapeutic levels of naturally-produced functional dystrophin protein within skeletal and cardiac muscle tissue

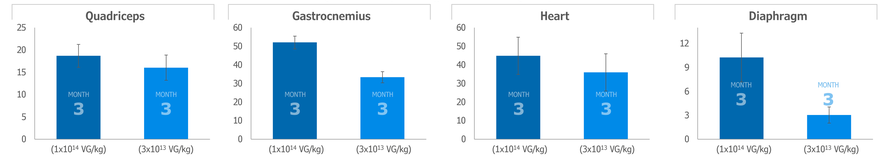
Durable dystrophin protein levels in skeletal and cardiac muscle tissue out to 9 months

Diaphragm and intercostal muscles contribute to respiratory function. We observed strong editing efficiency in the intercostals similar to other skeletal muscles (data not shown)

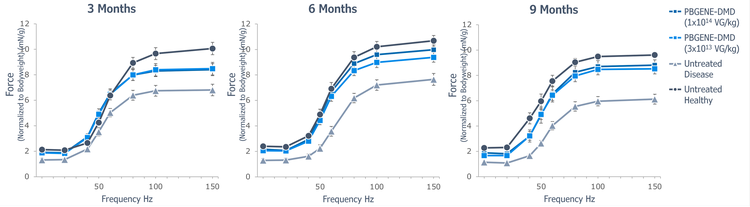
Broad and substantial functional dystrophin restoration across skeletal and cardiac muscle fibers



Percent of PBGENE-DMD Corrected Myofibers Expressing Functional Dystrophin in Treated Disease Mice at Month 3

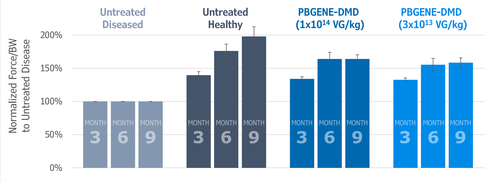


PBGENE-DMD Significantly Improves Muscle Function and Demonstrates Long-Term Durability



6-month timepoint shows an improvement in functional outcome vs. 3-month timepoint; Improvement in muscle force output is maintained out to 9 months post PBGENE-DMD treatment

Maximal Force Output 3- to 9-months



PBGENE-DMD-treated mice maintained 81-84% of the maximal force output and 89-92% tetanic force output observed in healthy mice through 9 months

1. Poyatos-Garcia et al. Ann Neurol, 2022 92(5):793-806. **2.** Takeda et al. J *Neuromuscul Dis*, 2021. 8(Suppl 2):S343-358. **3.** Shumizu-Motohashi et al. Orphanet J Rare Dis, 2018. 13(1):93. **4.** Mendell et al. *Nat Med*, 2024 31:332-341.
5. Hart et al. *JCI Insight*, 2024 9(11):e165869. **6.** Potter et al. Sci Rep, 2025 15(1):4. **7.** Taglia et al. Acta Myol. 2015. (1):9-13. **8.** Feraudy et al. Ann Neurol, 2021 Feb;89(2):280-292.