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Towards Development of a 'Silence and Replace' Based Approach for the Treatment of Oculopharyngeal Muscular Dystrophy

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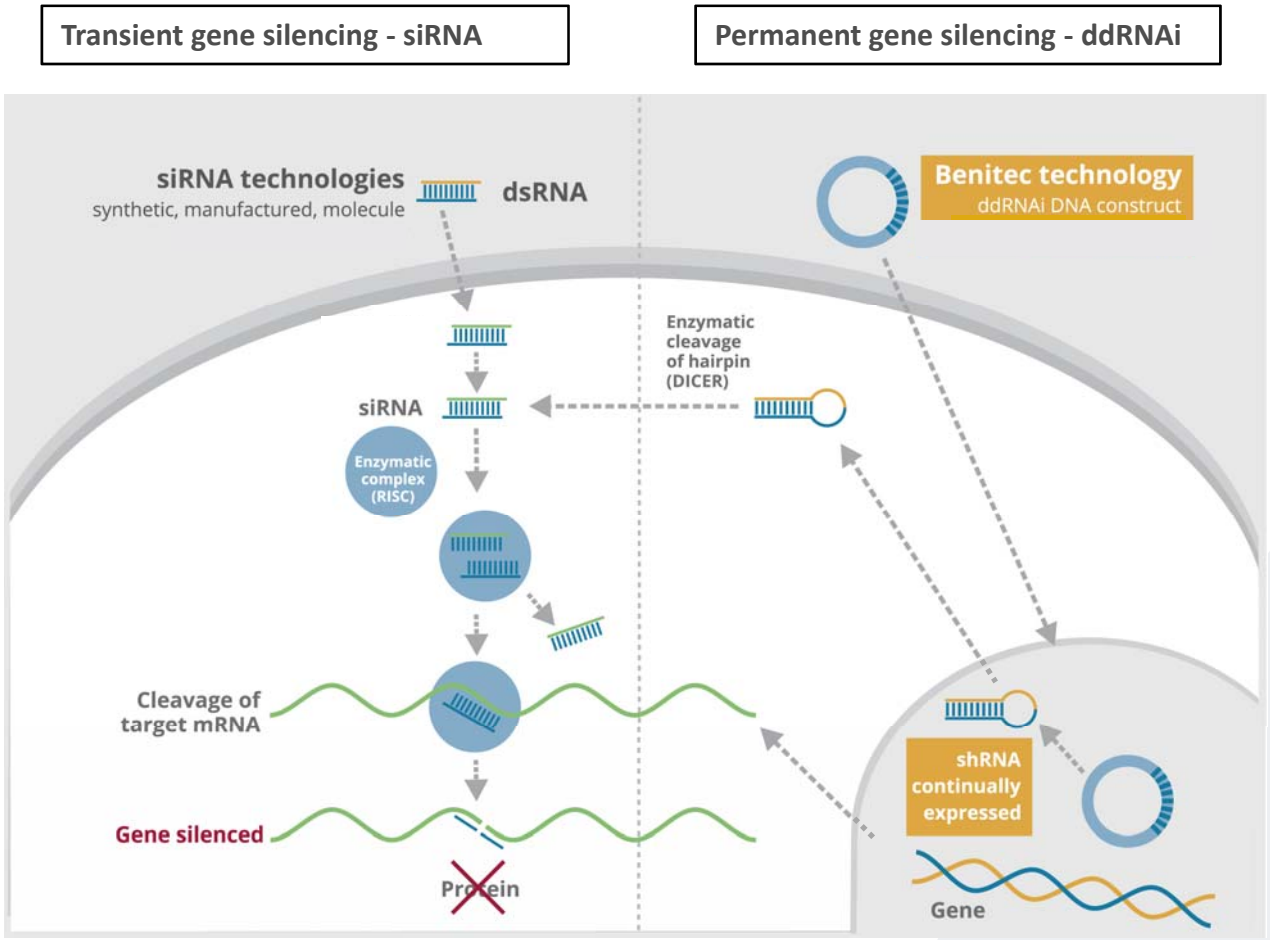
Permanent Gene Silencing via DNA-Directed RNA Interference (ddRNAi)

- Combines RNA interference with gene therapy delivery
- Long term therapeutic potential from a single administration
- Constant, steady state levels of shRNA expression
- Silence a single gene or target multiple genes simultaneously
- Simultaneous silencing of disease causing genes with co-expression of normal genes to restore function



Diverse Program Pipeline

Program	Delivery	Discovery	Preclinical	IND-Enabling	Early stage clinical (IND – Phase 2)	Late stage clinical (Phase 2 – Phase 3)	Commercial Rights
Orphan Disease – oculopharyngeal muscular dystrophy (OPMD)							
OPMD **BB-301**	AAV Intramuscular						• global

Oculopharyngeal Muscular Dystrophy

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Disease:

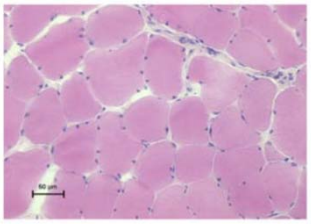
- Rare autosomal dominant inheritance
- 1:100,000 (Europe)
- As high as 1:600 in specific populations
- Typical age of onset is in 50's or 60's

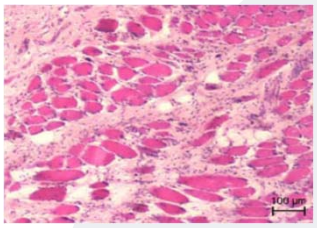
Characterized by:

- Eyelid drooping (ptosis)
- Swallowing difficulty (dysphagia)
- Proximal limb weakness
- Death due to aspiration pneumonia & malnutrition

Histopathology:

- Decrease of muscle fiber number
- Variation in the size of muscle fibers
- Fibrosis (connective tissue)



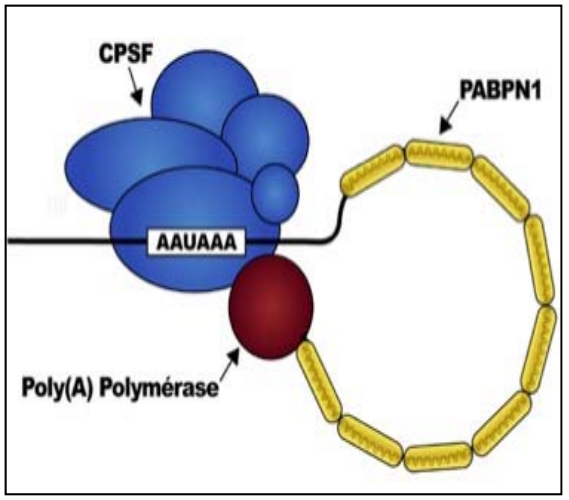


Non-affected **Affected**

Genetic Basis of OPMD: Expansion of the Poly-Alanine Tract Within PABPN1

PABPN1:

- A ubiquitous factor that promotes interaction between the poly(A) polymerase and CPSF (cleavage and polyadenylation specificity factor) and thus controls the length of mRNA poly(A) tails, mRNA export from the nucleus, and alternative poly(A) site usage.

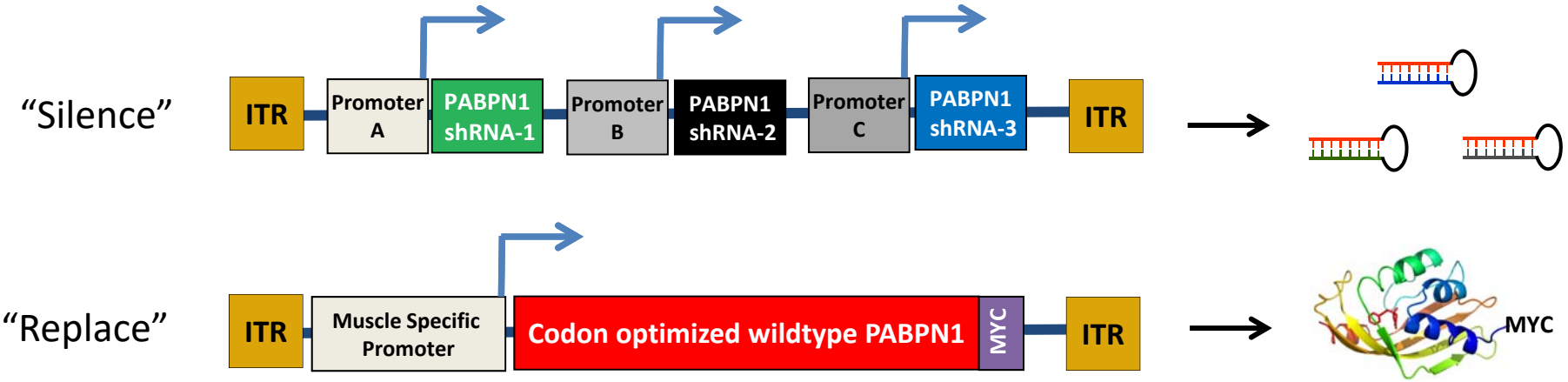


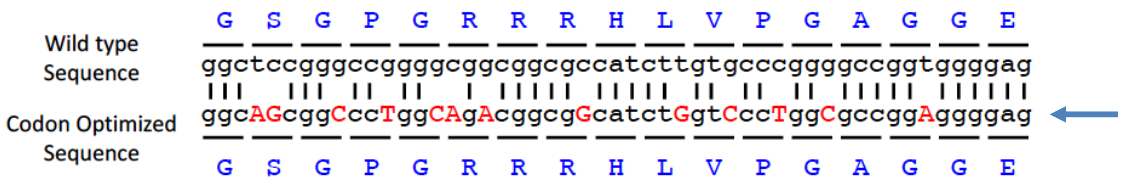
In OPMD:

- A genetic mutation results in trinucleotide repeat expansion within exon 1 of PABPN1 and results in an expanded poly-alanine tract at the N-terminal end of PABPN1.

WT ATG $(GCG)_6$ ----------$(GCA)_3$ GCG GGG GCT GCG..
MUT ATG $(GCG)_6$ $(GCG)_{1-7}$ $(GCA)_3$ GCG GGG GCT GCG…--

A Dual Vector Approach for a ddRNAi Treatment Against OPMD





Insensitive to shRNA

PABPN1 gene therapy for oculopharyngeal muscular dystrophy

A. Malerba[1,*], P. Klein[2,*], H. Bachtarzi[1,†], S.A. Jarmin[1], G. Cordova[2], A. Ferry[2,3], V. Strings[4], M. Polay Espinoza[2], K. Mamchaoui[2], S.C. Blumen[5], J. Lacau St Guily[2,6], V. Mouly[2], M. Graham[4], G. Butler-Browne[2], D.A. Suhy[4], C. Trollet[2,**] & G. Dickson[1,**]

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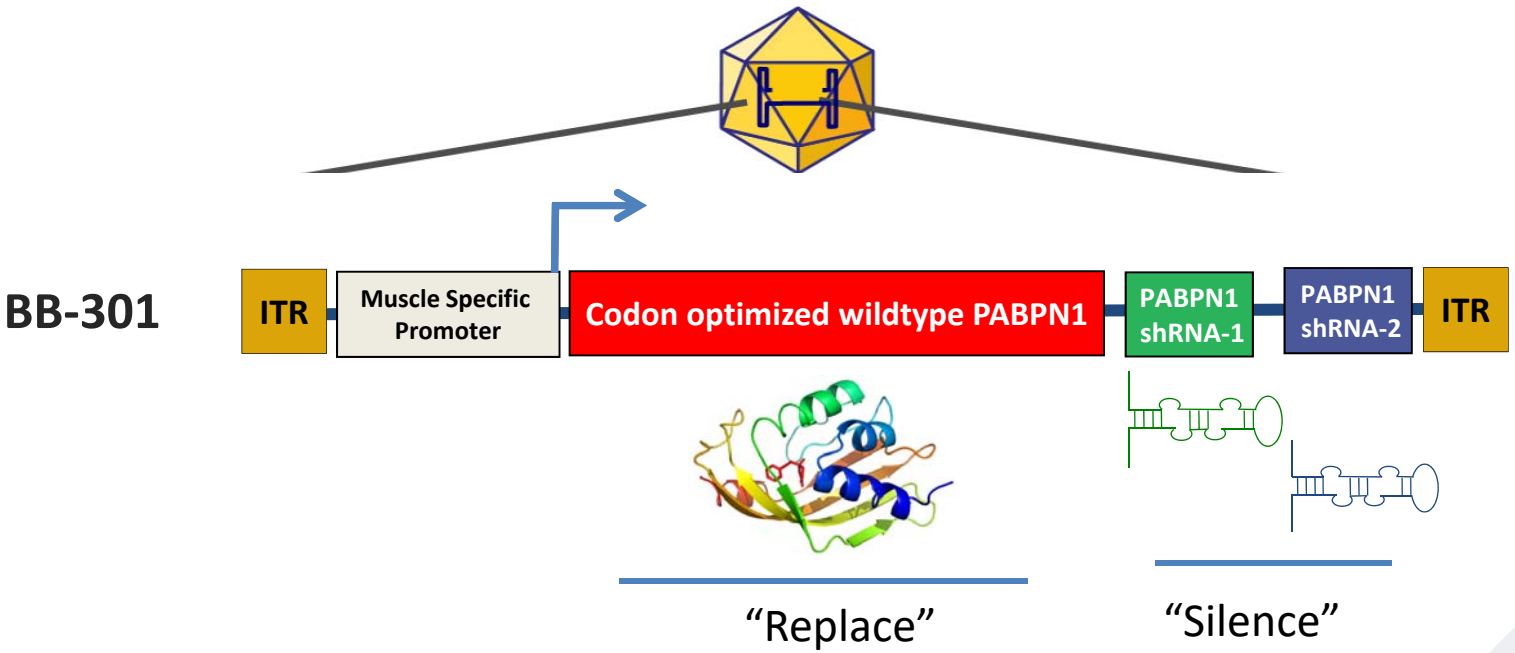
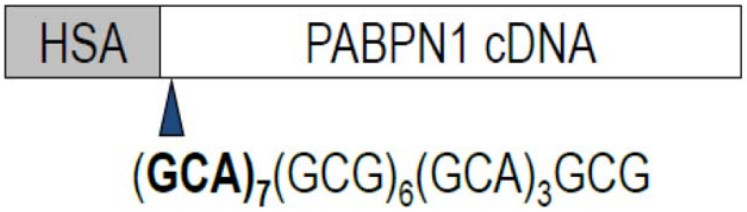
BB-301: A Single Vector 'Silence and Replace' Approach to Treat OPMD

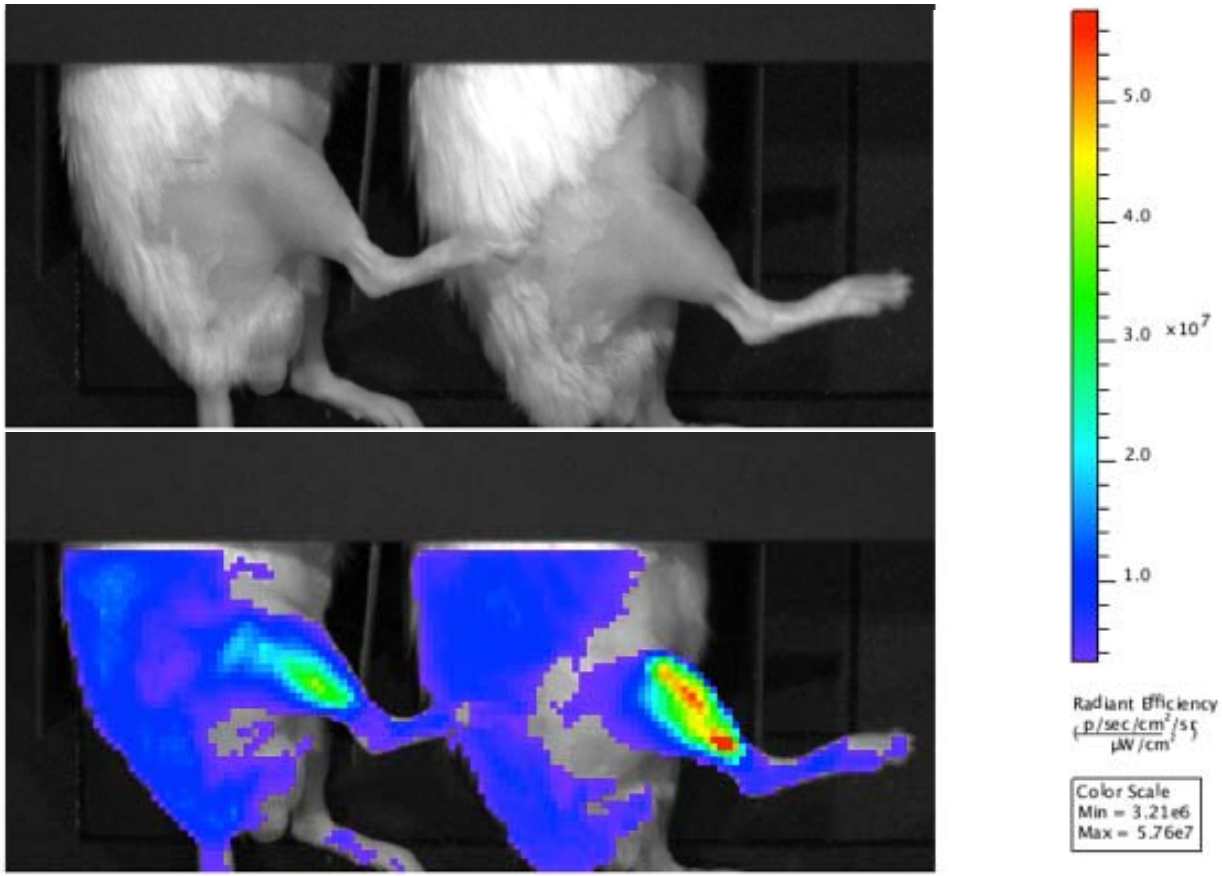


Pre-Clinical Model of OPMD: The 'A17' Mouse



- Transgenic mouse: express a mutated bovine PABPN1 driven by the human skeletal actin promoter in addition to the endogenous PABPN1
- Recapitulates severe muscle atrophy
- Mimics many of the disease pathologies:
  - Progressive muscle weakness/ atrophy
  - Fibrosis
  - Mitochondrial / Ubiquitin-Proteasome defects
  - Muscles contain intranuclear inclusions

BB-301: Use of AAV / Intramuscular Injections



BB-301 Treatment Inhibits Diseased Gene Expression & Restores Wildtype PABPN1 Levels in A17 Mice

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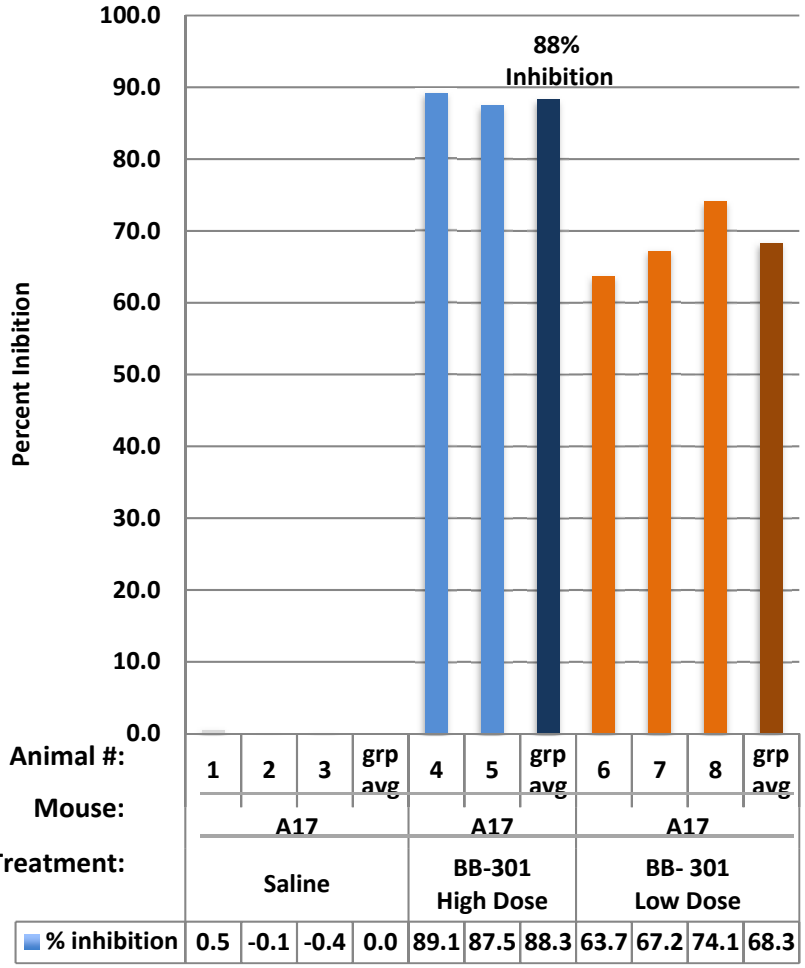
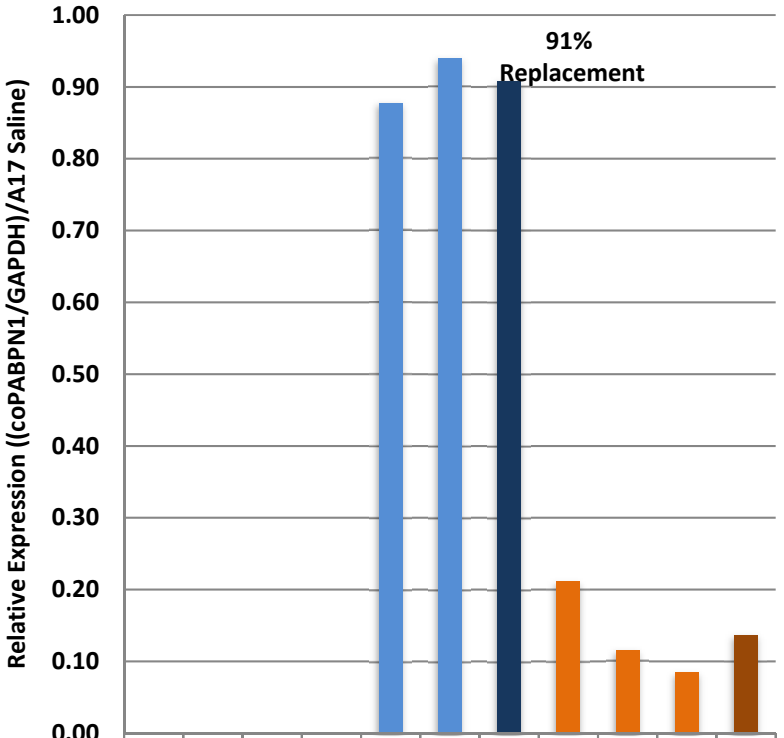
SILENCE: Inhibition of PABPN1 Expression



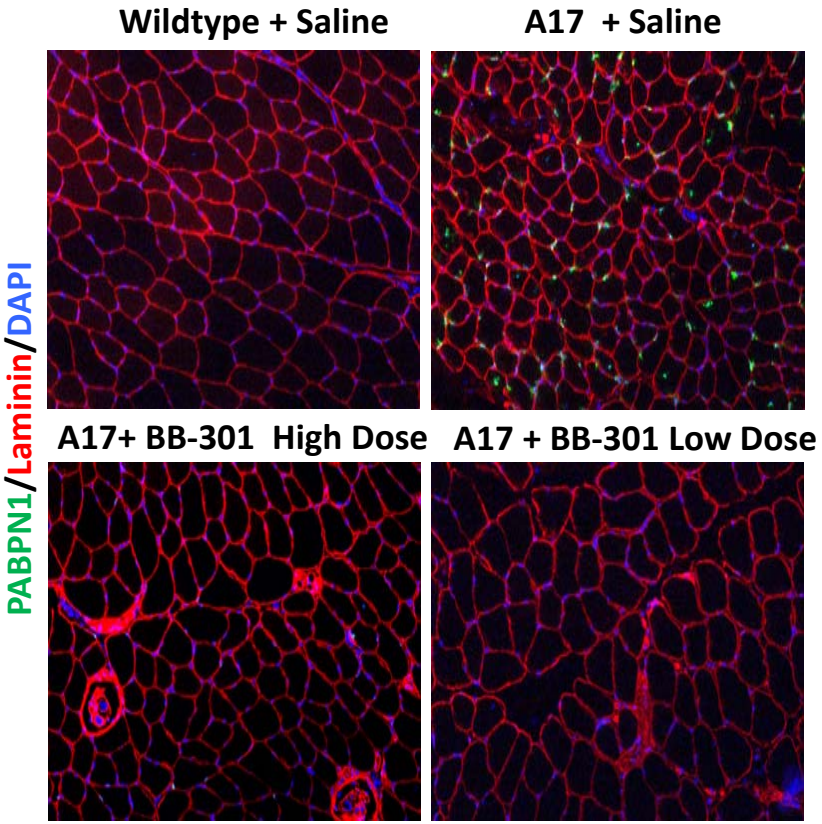
Animal #:	1	2	3	grp avg	4	5	grp avg	6	7	8	grp avg
Mouse:	A17				A17			A17			
Treatment:	Saline				BB-301 High Dose			BB- 301 Low Dose			
% inhibition	0.5	-0.1	-0.4	0.0	89.1	87.5	88.3	63.7	67.2	74.1	68.3

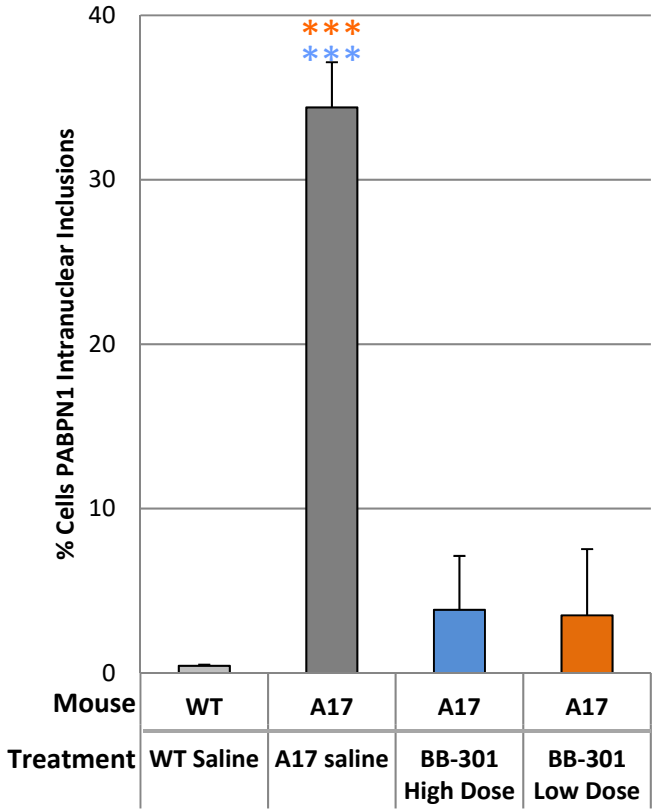
REPLACE: Codon-Optimized PABPN1 Expression



Animal #:	1	2	3	grp avg	4	5	grp avg	6	7	8	grp avg
Mouse:	A17				A17			A17			
Treatment:	Saline				BB-301 High Dose			BB-301 Low Dose			
rel exp	0.00	0.00	0.00	0.00	0.88	0.94	0.91	0.21	0.11	0.08	0.14

BB-301 Treatment Resolves Intranuclear Inclusions in A17 Mice





BB-301 Treatment Reduces Fibrosis in Transverse Muscle Section of A17 Mice

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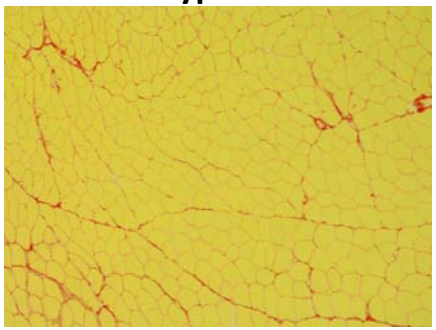
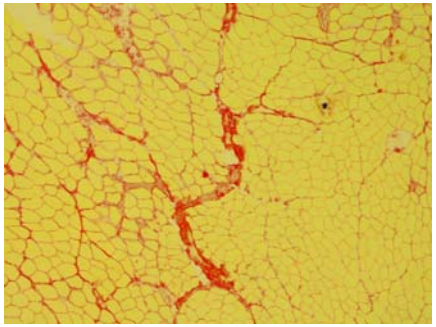
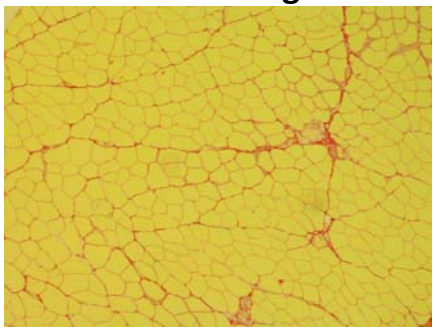
Wildtype + Saline



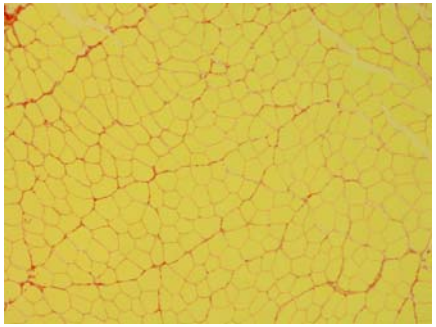
A17 + Saline

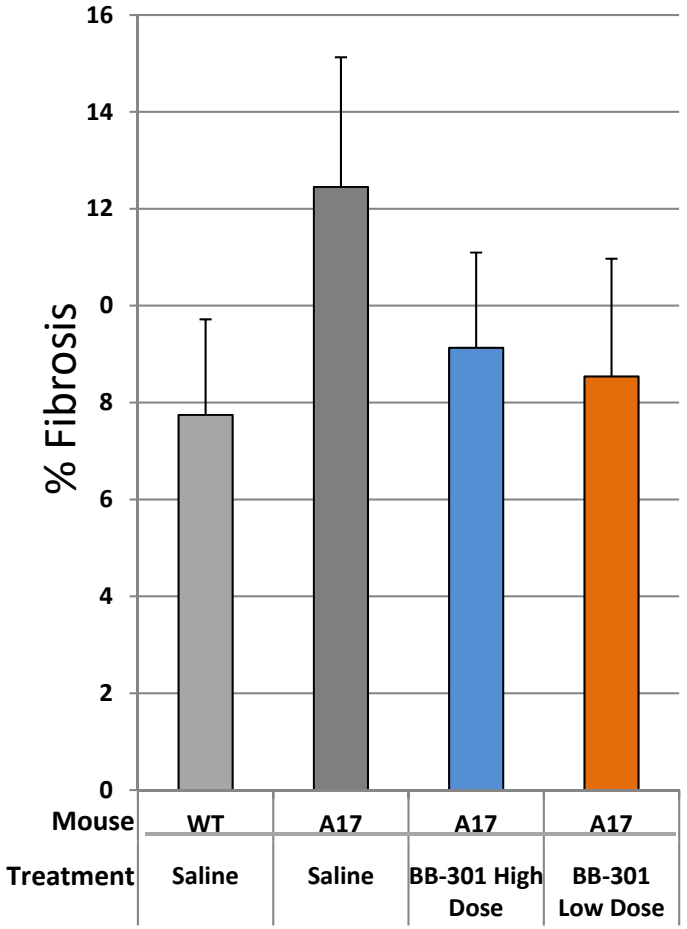


A17+ BB-301 High Dose



A17 + BB-301 Low Dose





BB-301 Treatment Restores Muscle Force and Muscle Weight in A17 Mice

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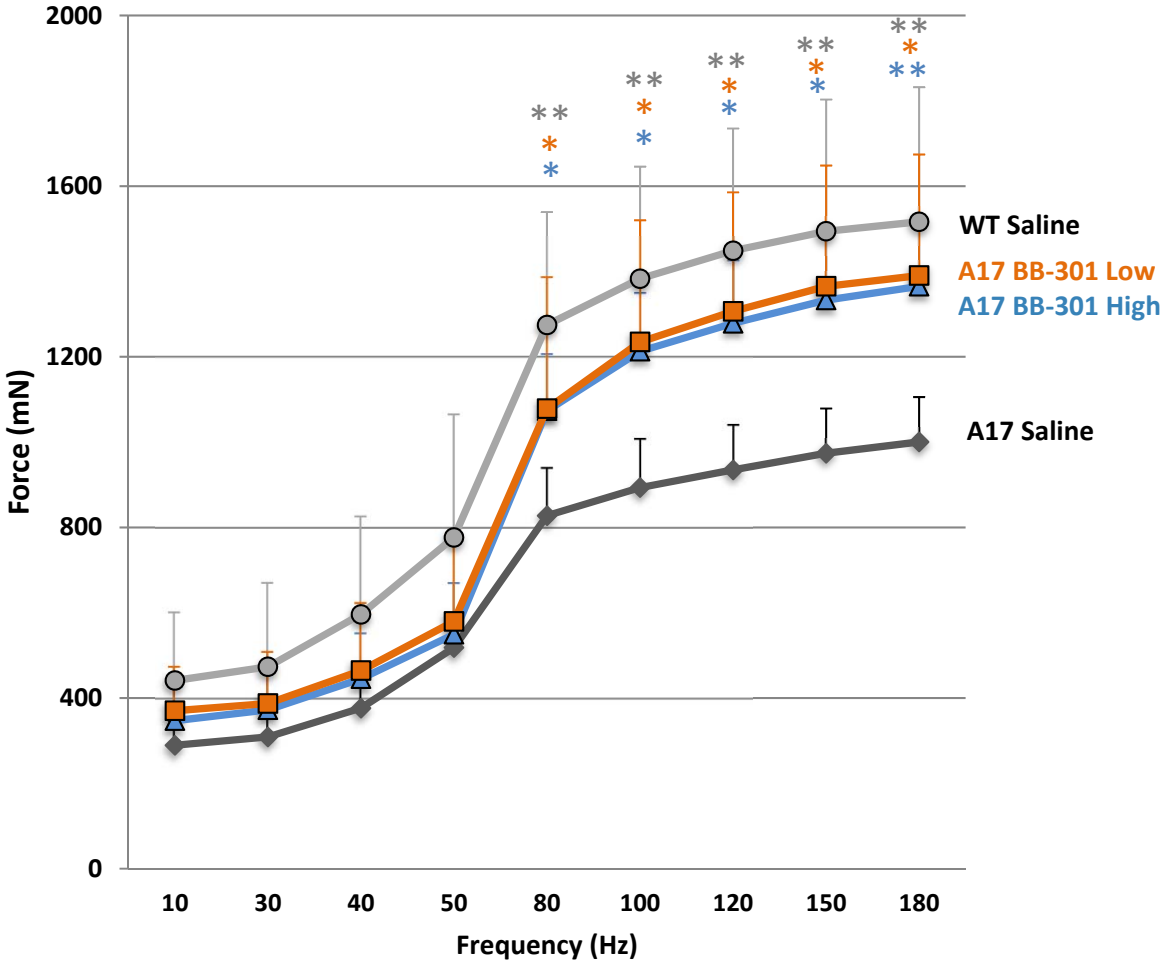
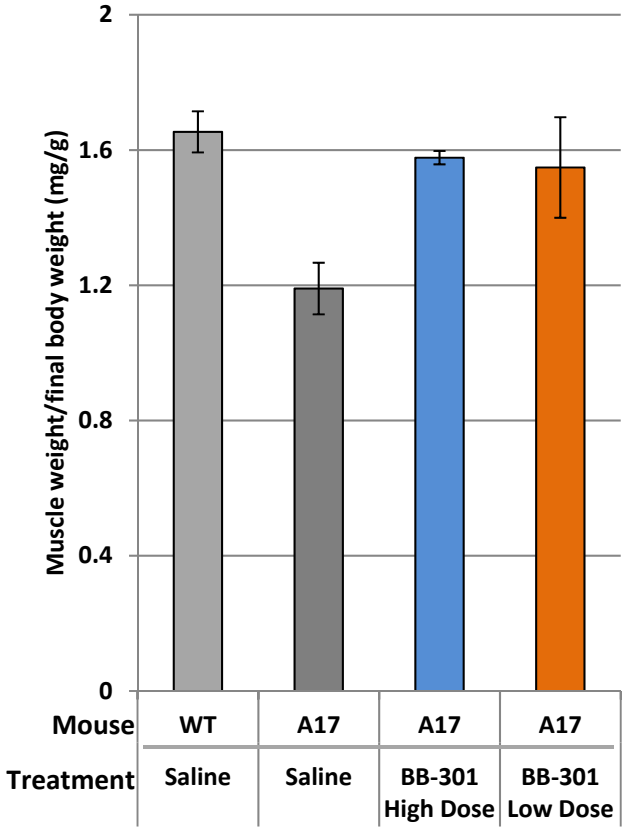
Restoration of Muscle Force



Restoration of Muscle Weight



Summary

Developed a single vector "silence and replace" based approach to treat OPMD

- Uses a bi-functional RNA to produce shRNA to inhibit PABPN1 including the expanded PABPN1 protein as well as expresses a codon optimized normal copy of PABPN1
- Simplifies the manufacturing and clinical development

Treatment of A17 mice with BB-301:

- Efficiently 'silences' mutated PABPN1 and 'replaces' codon optimized PABPN1
- Reduces insoluble intranuclear aggregates
- Decreases fibrosis
- Improves muscle strength
- Recovers muscle mass

Oculopharyngeal Muscular Dystrophy
Clinical Candidate BB-301: Product Overview

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Oculopharyngeal Muscular Dystrophy	• Rare, autosomal dominant, monogenic disease • Estimated 12,000 patients in Western countries • Characterized by eye lid drooping, swallowing difficulties, proximal limb weakness, death due to aspiration pneumonia and malnutrition
BB-301 Product Profile	• Designed to treat dysphagia associated with OPMD • 'Silence and Replace' – unique gene therapy mechanism • Silence: Inhibits mutant PABPN1 gene • Replace: Simultaneously reintroduces normal PABPN1 gene to restore function
Value / Commercial Opportunity	• Near-term value inflection point: 2H18 clinic entry • Significant unmet medical need with no direct competition • Orphan status provides expeditious and cost efficient commercialization path • Commercial opportunity potentially in excess of US$1 billion • Potential for silence and replace approach for other monogenic disorders

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