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NASDAQ: BNTC | ASX: BLT

BB-301: A SINGLE "SILENCE AND REPLACE" AAV-BASED VECTOR FOR THE TREATMENT OF OCULOPHARYNGEAL MUSCULAR DYSTROPHY (OPMD)

David Suhy, Chief Scientific Officer

SAFE HARBOR STATEMENT

If we make any forward-looking statements, we note that such statements involve risks and uncertainties relating to the difficulties in our plans to develop and commercialize our product candidates, the timing of the initiation and completion of preclinical and clinical trials, the timing of patient enrolment and dosing in clinical trials, the timing of expected regulatory filings, the clinical utility and potential attributes and benefits of ddRNAi and our product candidates, potential future out-licenses and collaborations, our intellectual property position and the ability to procure additional sources of financing.

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DISCLOSURE

David Suhy is employed as Chief Scientific Officer of Benitec Biopharma and receives compensation in the form of salary and stock options

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OCULOPHARYNGEAL MUSCULAR DYSTROPHY: OVERVIEW

Disease:

- Rare autosomal dominant inheritance
- 1:100,000 (Europe)
- As high as 1:600 in specific populations
- Estimated as many as 12,000 treatable patients
- Typical age of onset is in late 40's with overt symptoms 50's or 60's

Characterized by:

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

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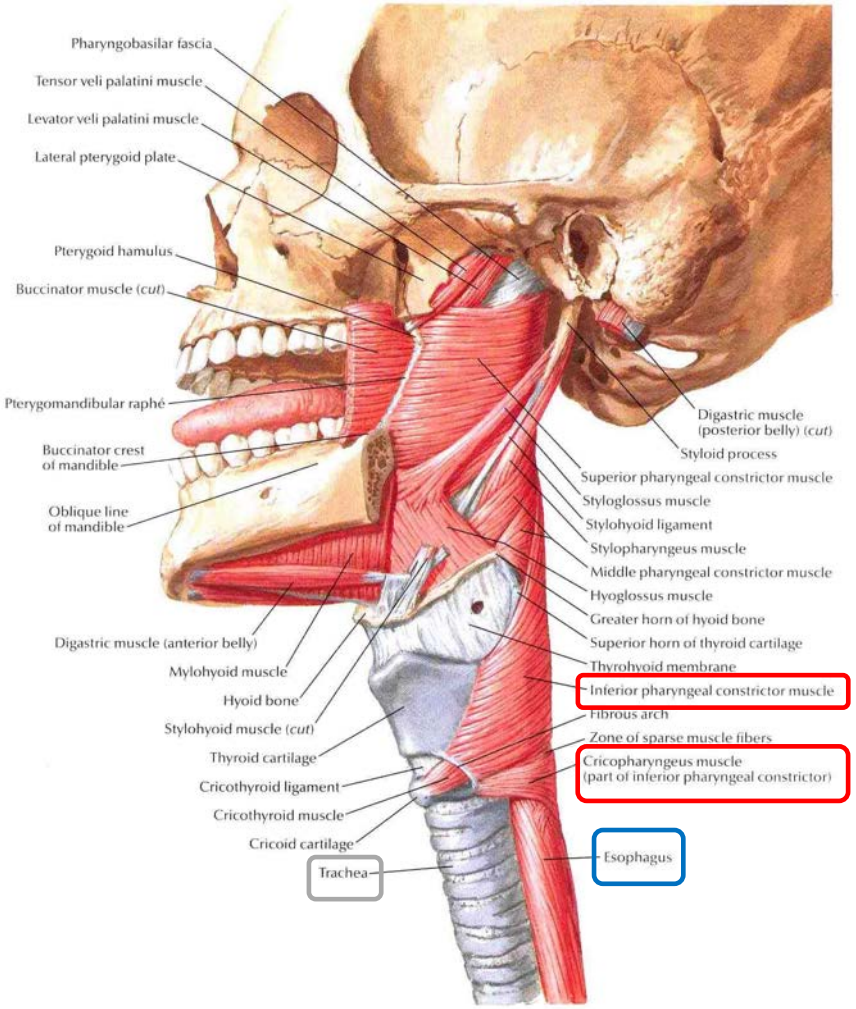
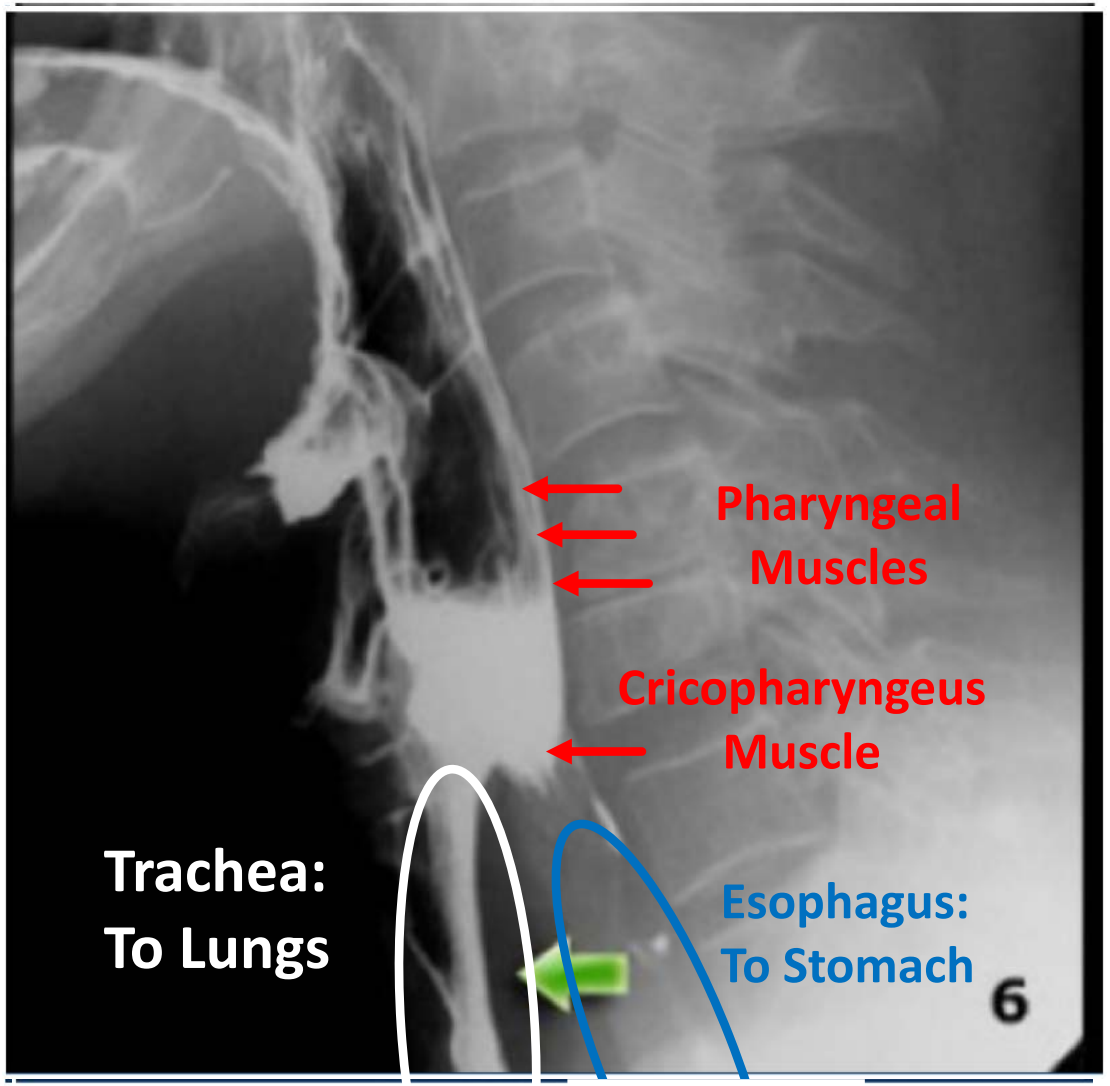
ASPIRATION FROM DYSPHAGIA





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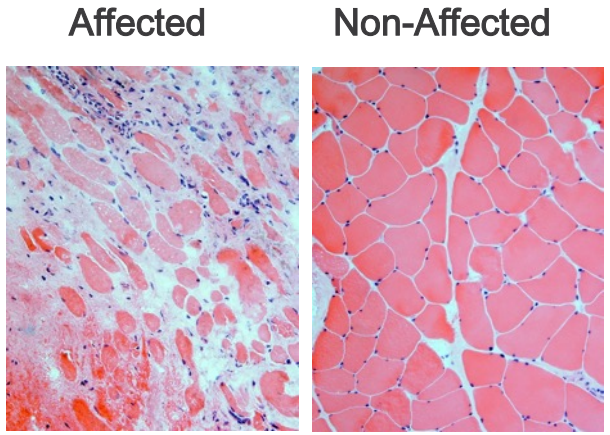
TISSUE AND MOLECULAR ASPECTS OF OPMD

Histopathology:

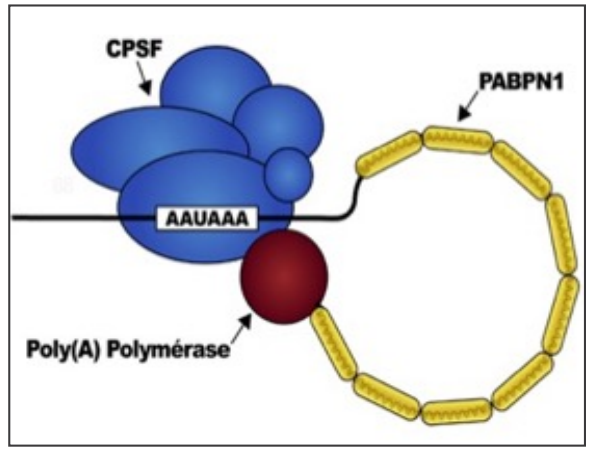
- Decrease of muscle fiber number
- Variation in the size of muscle fibers
- Fibrosis (connective tissue)

- Net effect: decrease in muscle force



PABPN1:

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



In OPMD:

- An autosomal dominant mutation results in trinucleotide repeat expansion in PABPN1

Normal	**ATG $(GCG)_6$ ---------- -$(GCA)_3$ GCG GGG GCT GCG…**
OPMD	**ATG $(GCG)_6$ $(GCG)_{1\text{-}7}$ $(GCA)_3$ GCG GGG GCT GCG…**

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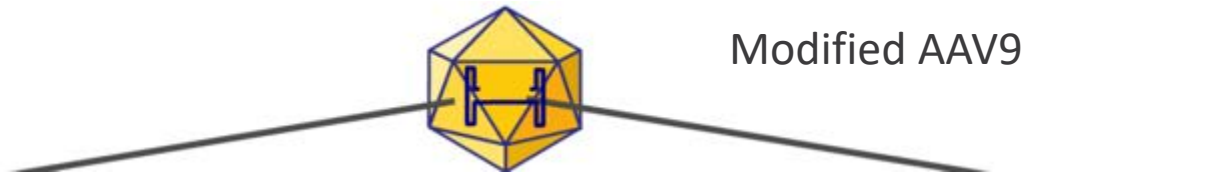
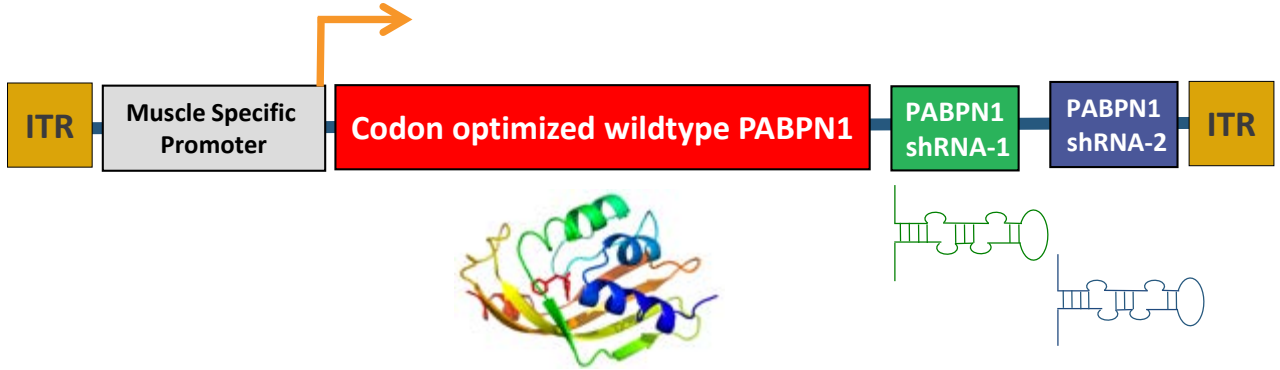
BB-301: A 'SILENCE AND REPLACE' BASED APPROACH



BB-301



← Insensitive to shRNA

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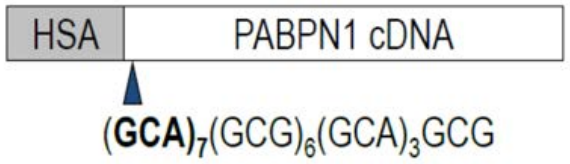
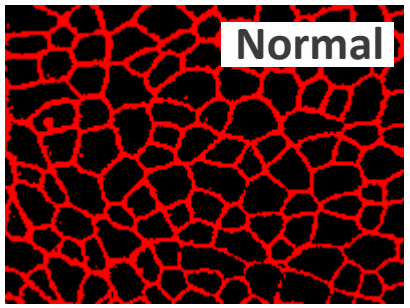
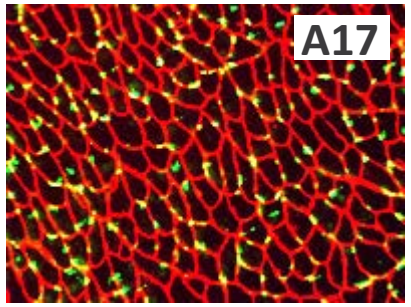
PRE-CLINICAL MODEL OF OPMD: THE 'A17' MOUSE



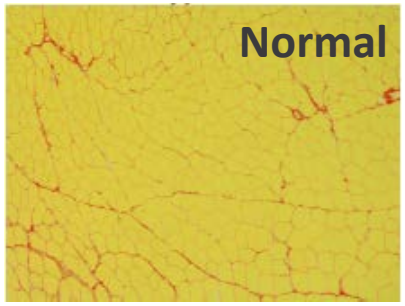
- Transgenic mouse: express a mutated bovine PABPN1 driven by the human skeletal actin promoter in addition to the endogenous PABPN1
- Recapitulates severe muscle atrophy
- Mimics many of the disease pathologies

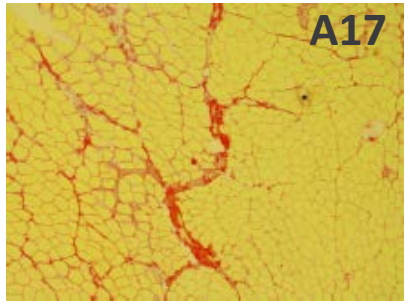
Intra Nuclear Inclusions (INI)



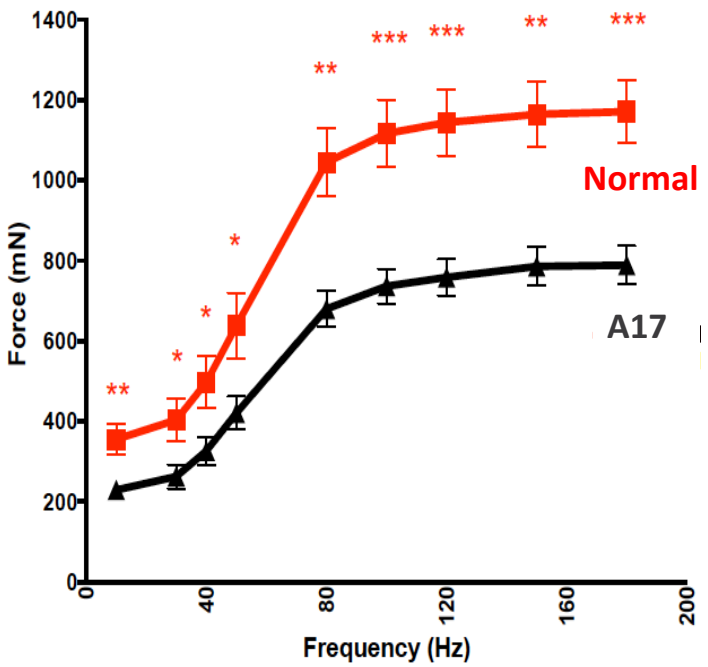


Fibrosis

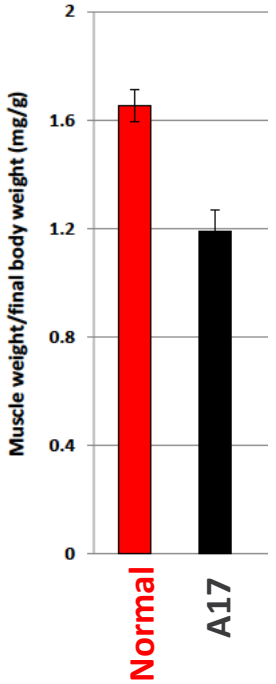




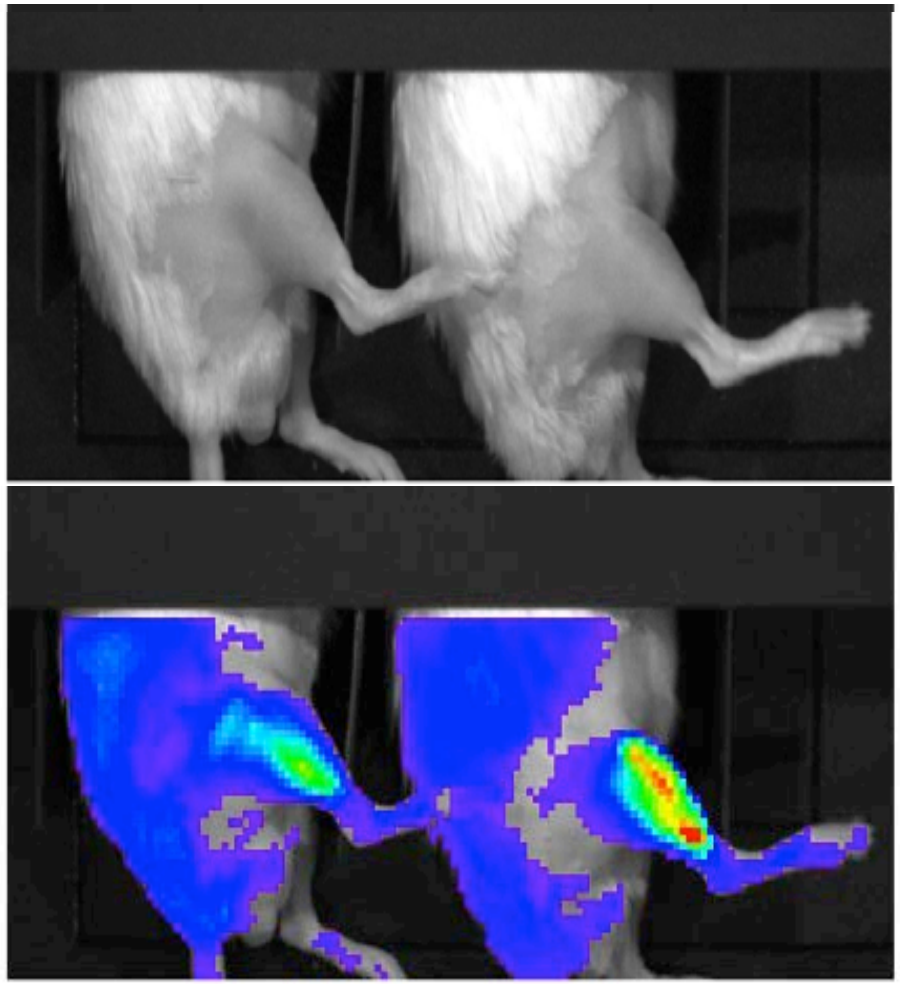
Muscle Force

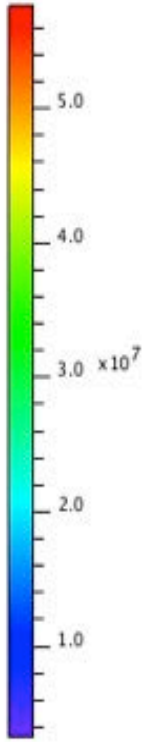


Muscle Weight

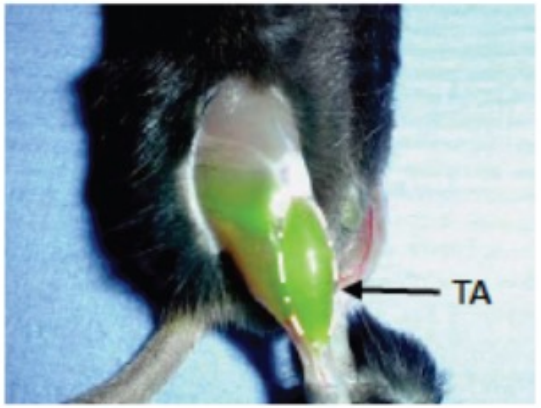


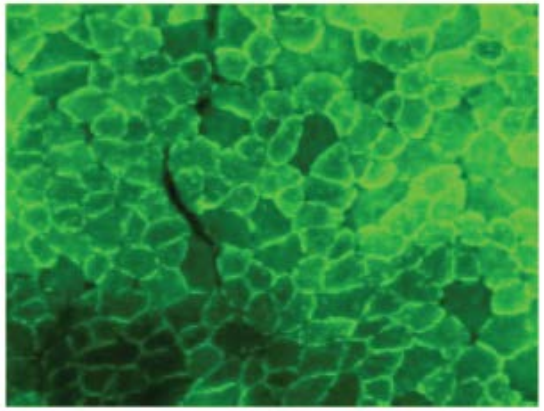
AAV TRANSDUCTION OF MUSCLE BY LOCAL INJECTION





muscle expressing GFP
1 year + post injection





Courtesy of G. Dickson, RHUL

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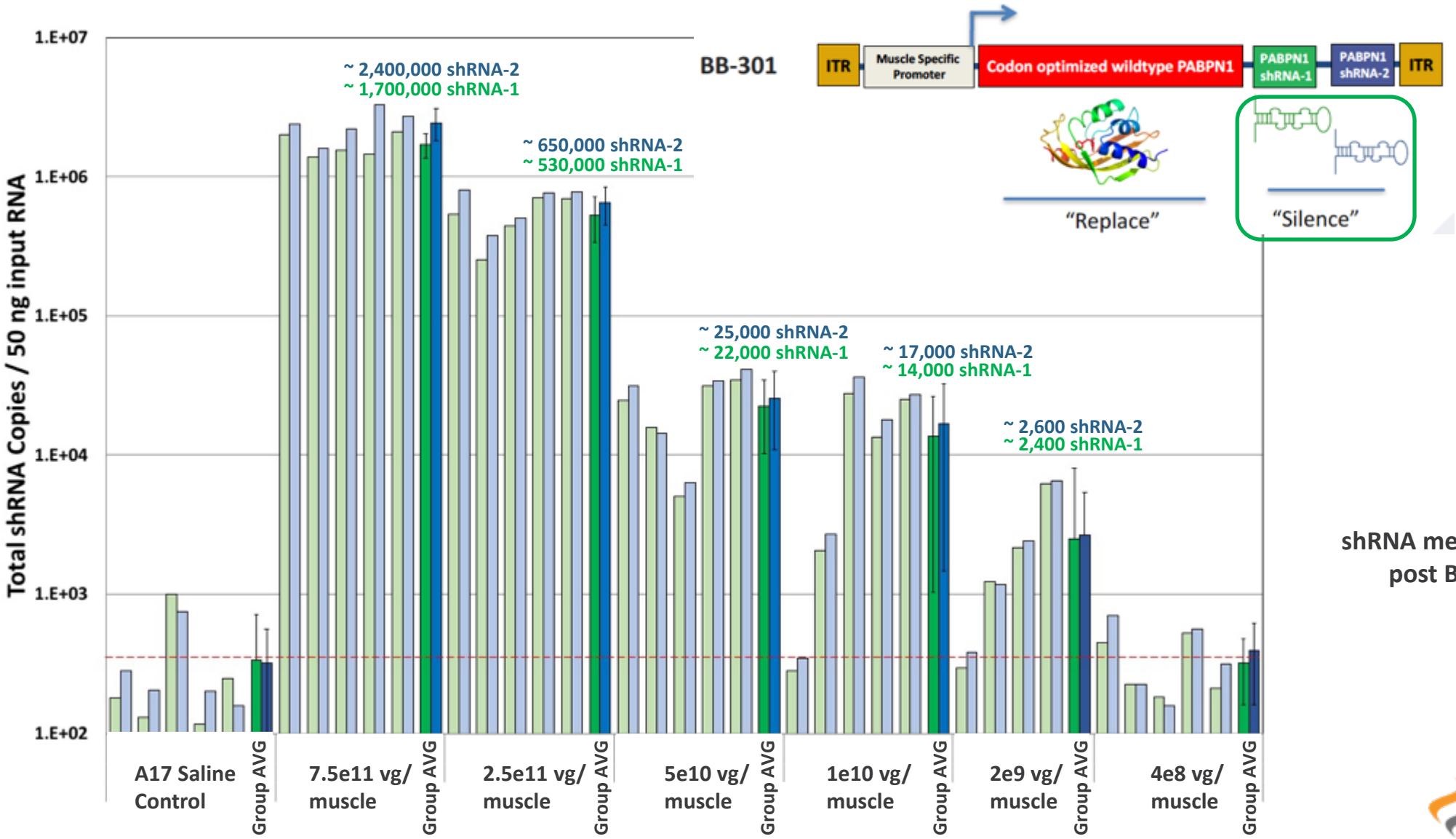
BB-301: DOSE RANGE FINDING STUDY - OVERVIEW

- Single doses of BB-301 across broad range: 4e8 vg/muscle up to 7.5e11 vg/muscle
- Each cohort had N=5 animals
- 2 doses per animal – left/right TA muscle
- Transgenic animals were 10-12 weeks at dosing with established OPMD phenotypes

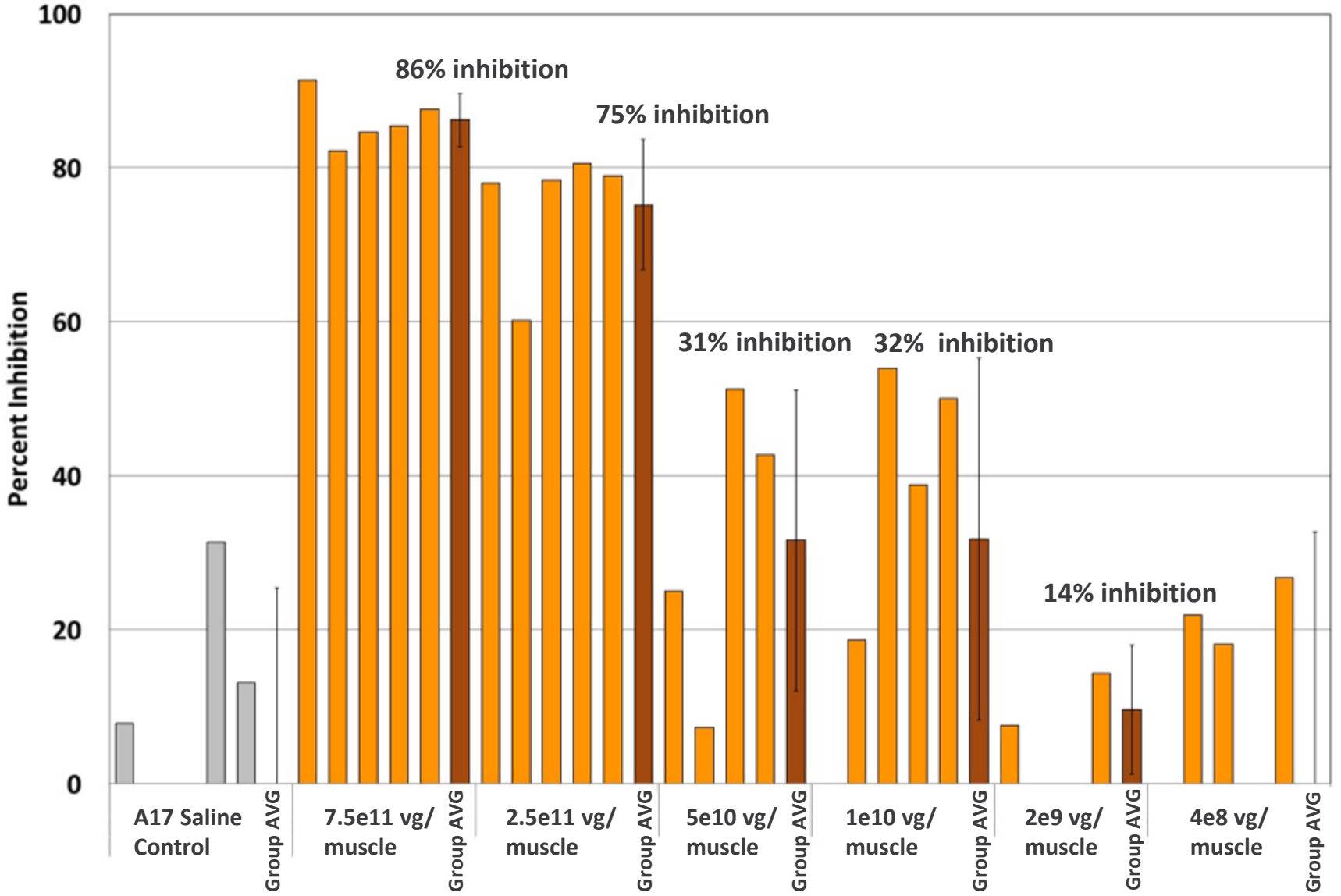
- Endpoint parameters monitored 14 weeks post dosing
- Individual muscles used for INIs, strength, weight
- Paired Muscles measured for shRNA production, codon optimized PABPN1 expression

BB-301: EXPRESSION OF SHRNA IN TA MUSCLES OF A17 MICE



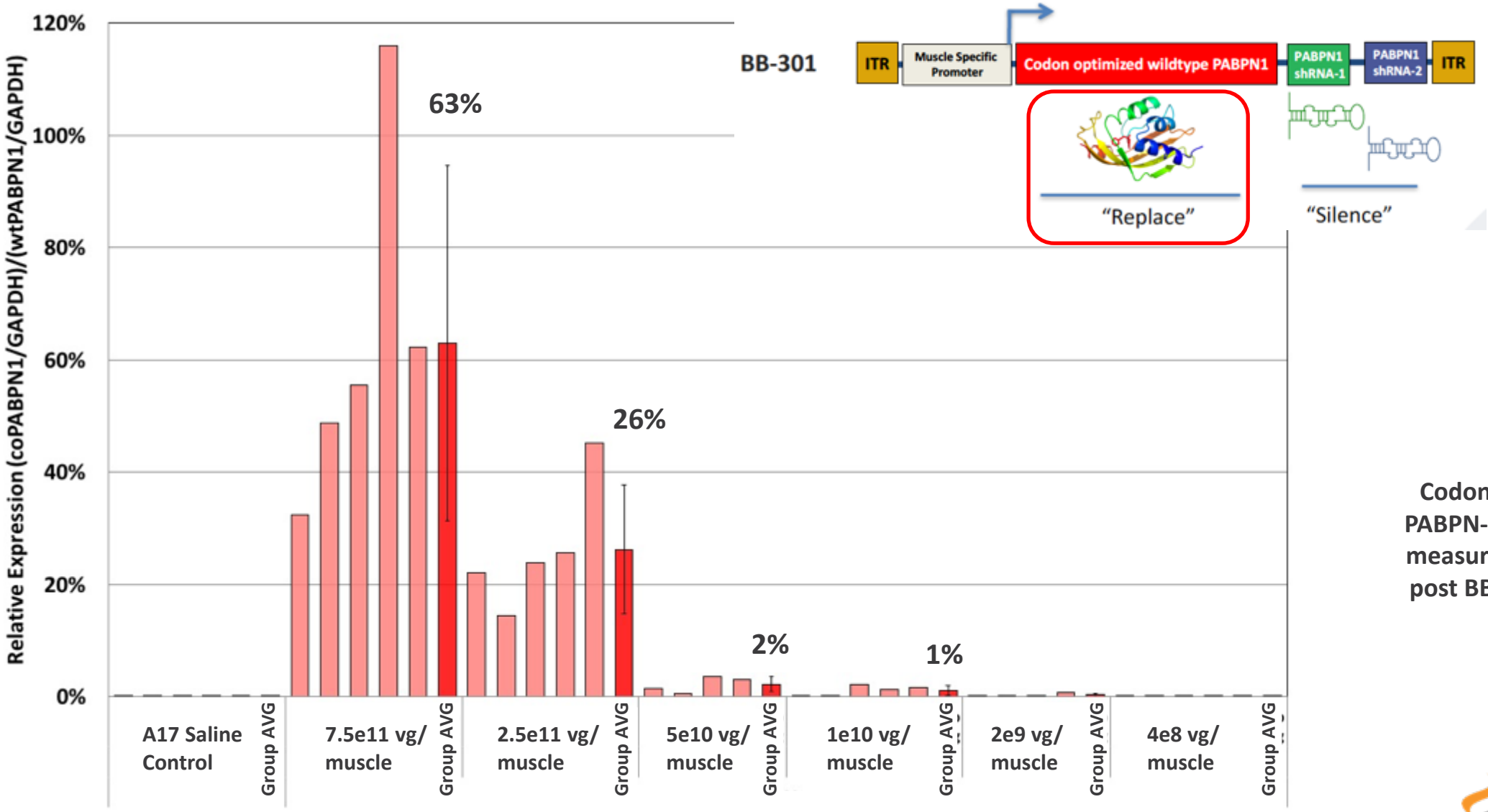
shRNA measured 14 weeks post BB-301 dosing

BB-301 SILENCES PABPN1 EXPRESSION (INCLUDING MUTANT PABPN1) IN AN OPMD MOUSE MODEL



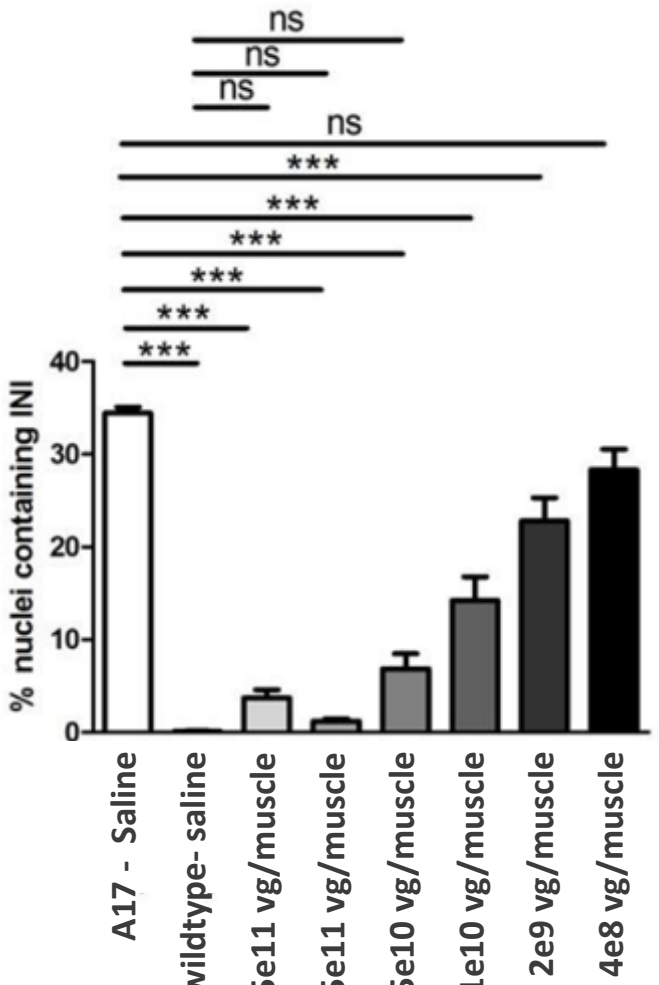
PABPN-1 Inhibition measured 14 weeks post BB-301 dosing

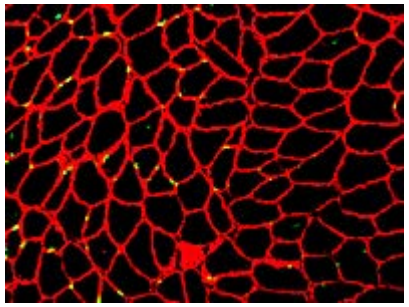
BB-301 RESTORES NORMAL PABPN1 LEVELS IN A17 MOUSE MODEL



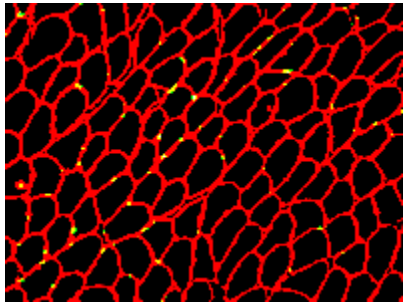
Codon Optimized PABPN-1 expression measured 14 weeks post BB-301 dosing

BB-301 REVERSES INTRANUCLEAR INCLUSIONS IN A17 MOUSE MODEL

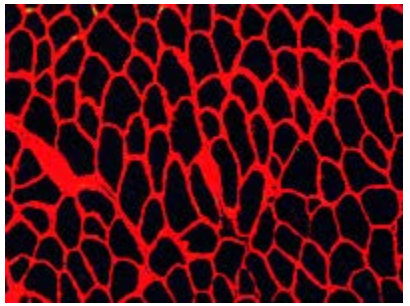




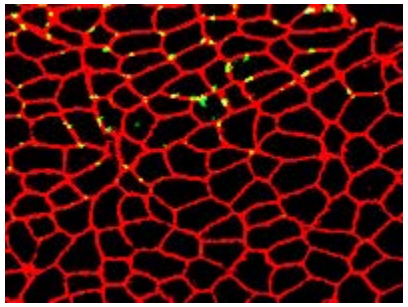
7.5e11 vg/muscle



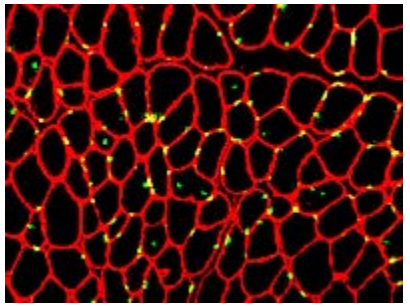
2.5e11 vg/muscle



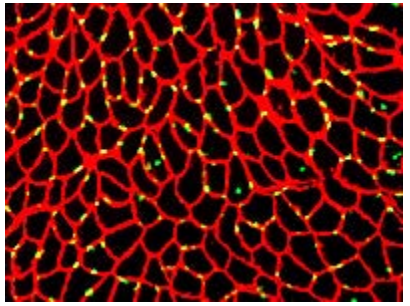
5e10 vg/muscle



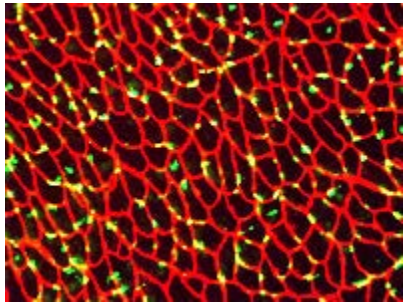
1e10 vg/muscle



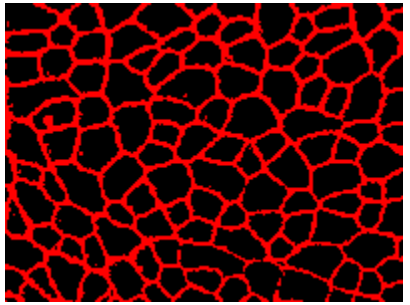
2e9 vg/muscle



4e8 vg/muscle



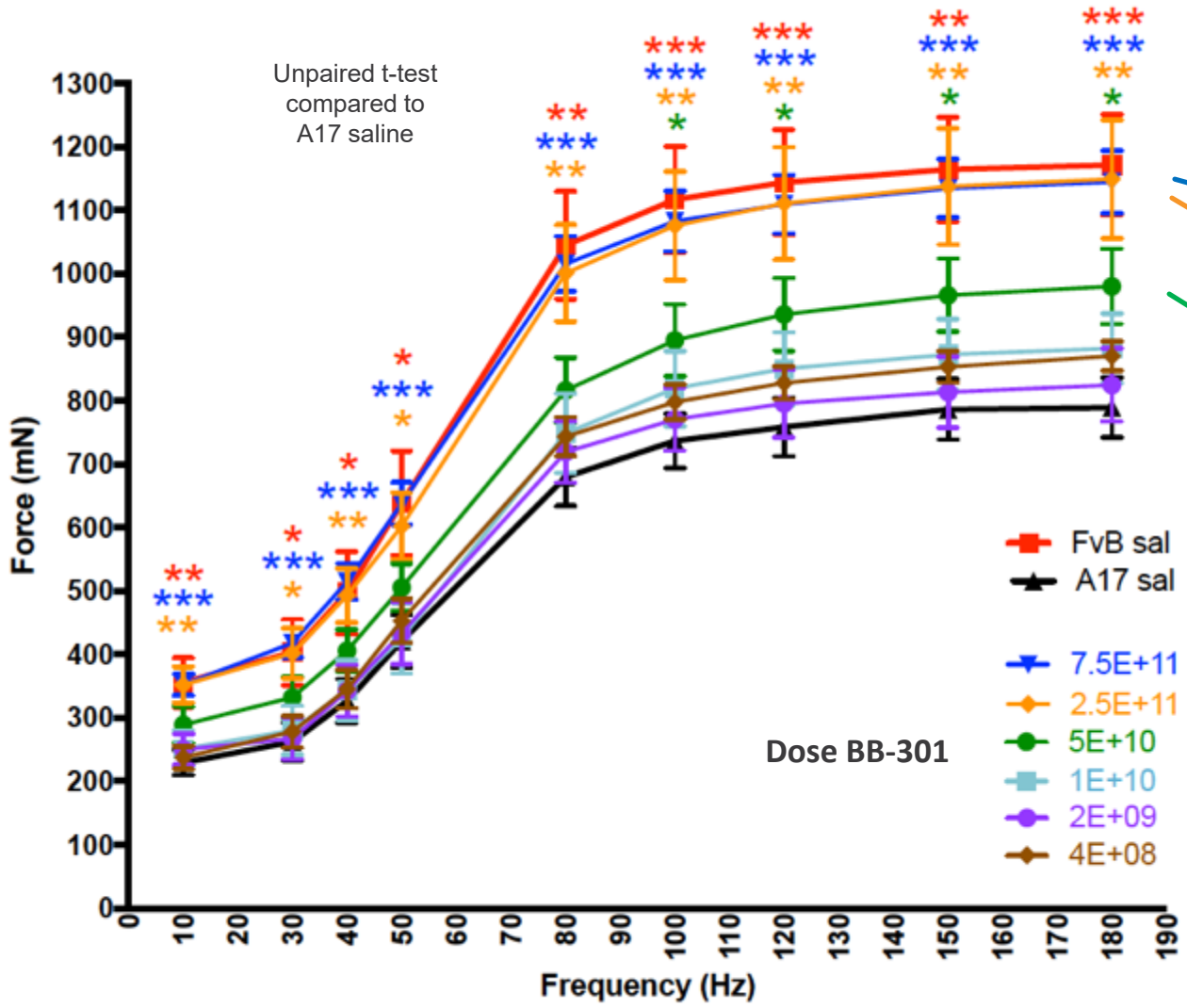
A17 - Saline



Wildtype- saline

INI persistence measured 14 weeks post BB-301 dosing

BB-301 RESTORES MUSCLE FORCE IN OPMD MOUSE MODEL



	"Silence"	"Replace"
BB-301 Dose (vg)	Inhibition PABPN1*	WT-PABPN1 Expression
7.5e11	86 %	63 %
2.5e11	75 %	26 %
5e10	31 %	2 %
1e10	32 %	1 %
2e9	14 %	0 %
4e8	0 %	0 %

Force measured 14 weeks post BB-301 dosing

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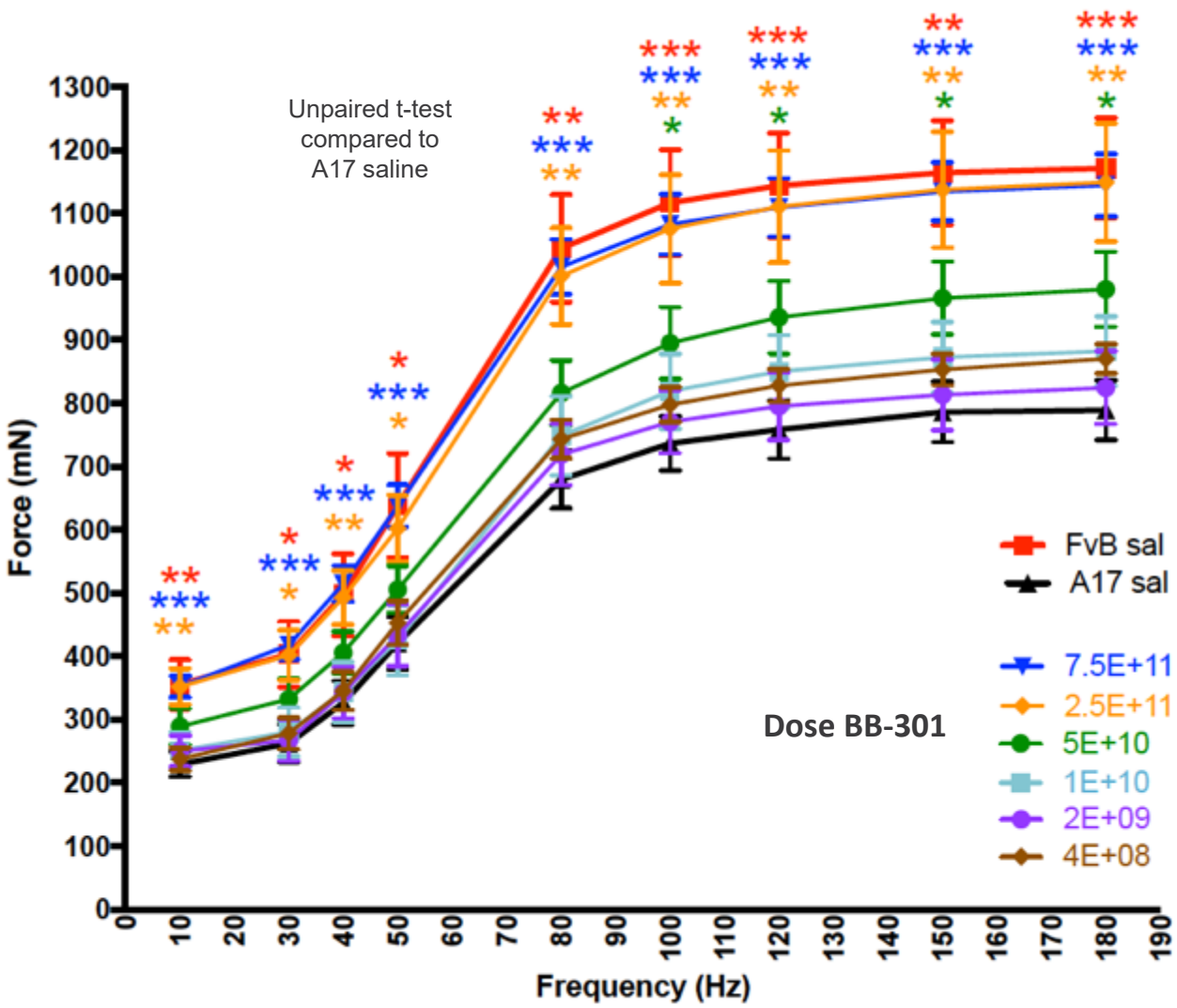
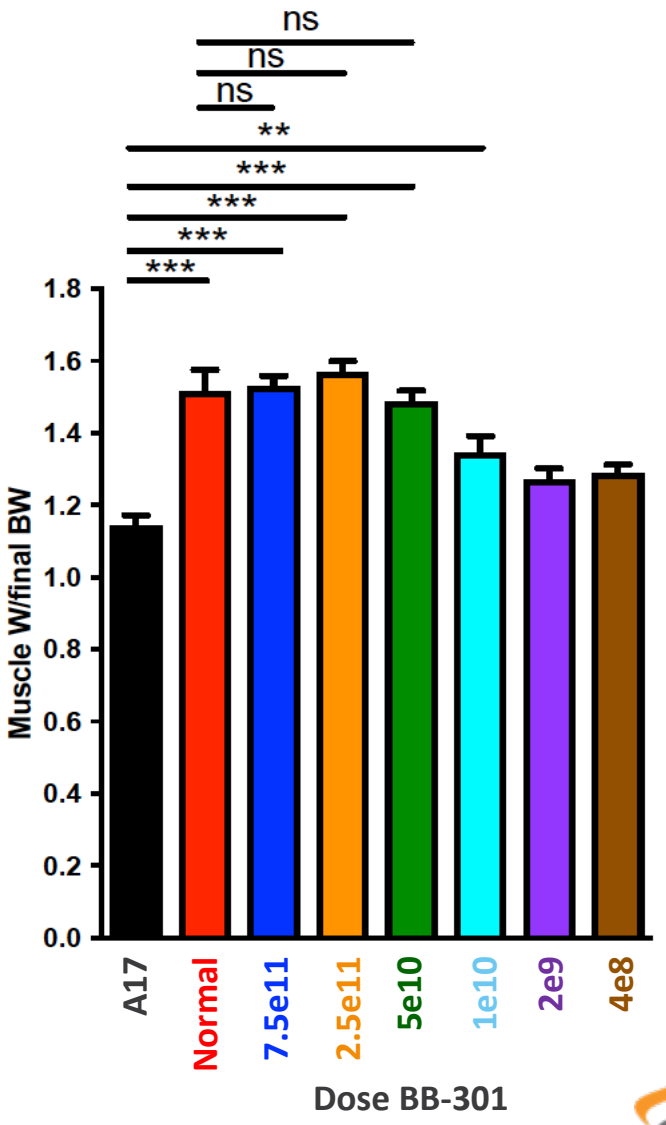
CORRELATION BETWEEN RESTORATION OF MUSCLE FORCE AND MUSCLE WEIGHT UPON BB-301 TREATMENT

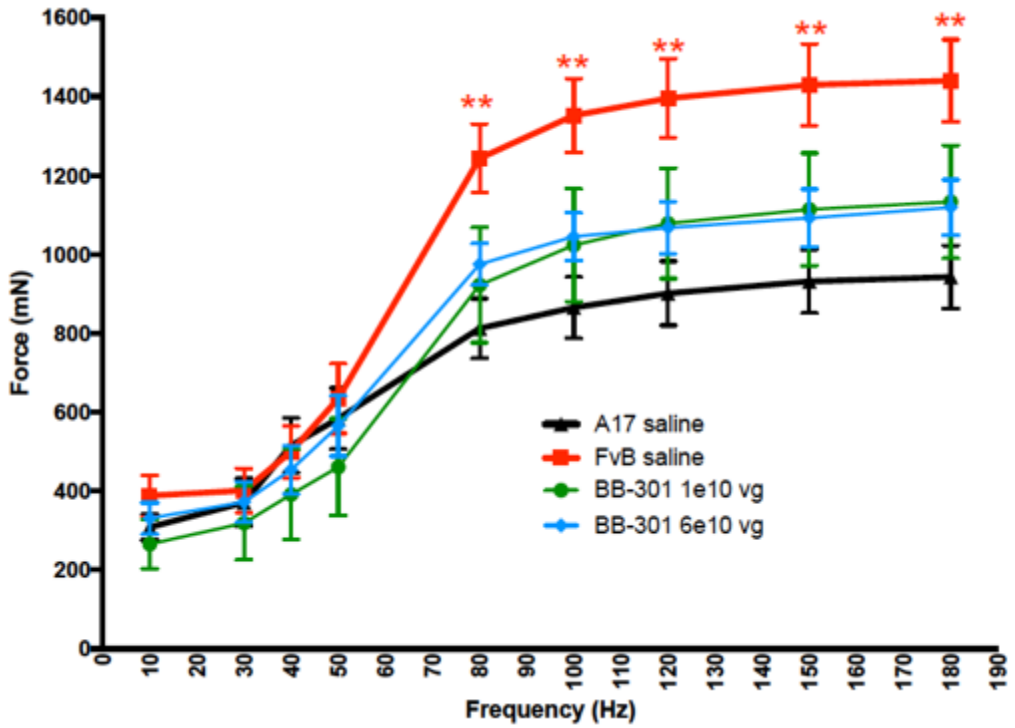




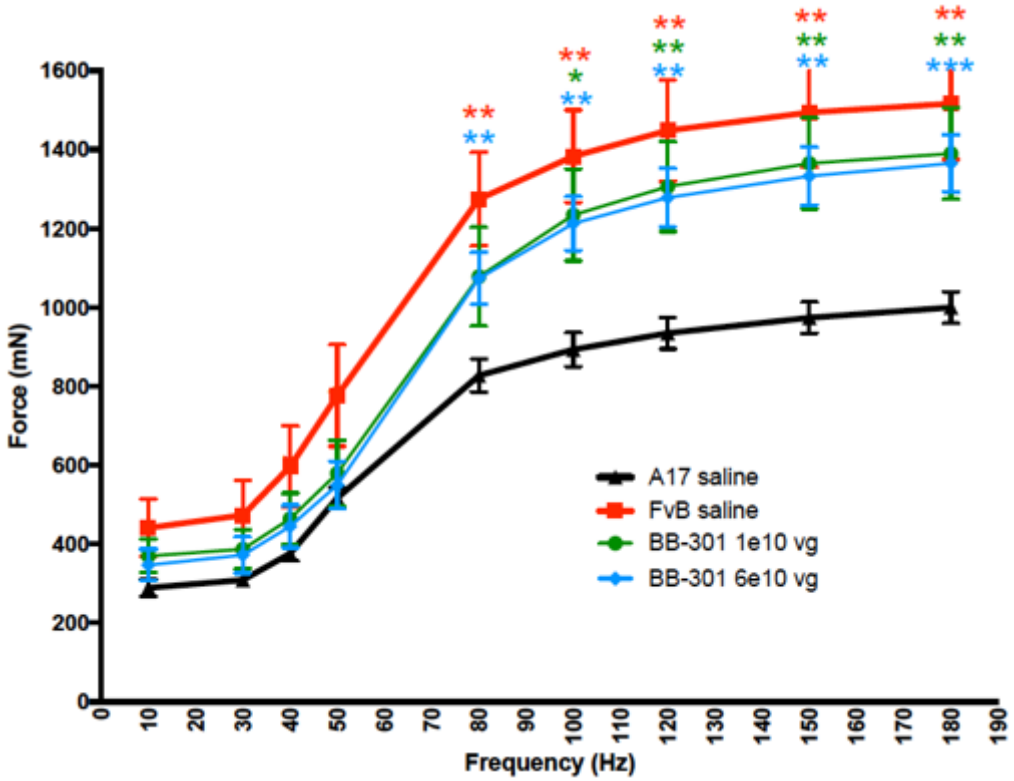
Muscle Weight

BB-301: RESTORATION OF MUSCLE FUNCTION TAKES TIME

14 weeks post BB-301 Dosing



20 weeks post BB-301 Dosing



BB-301 Dose (vg)	Inhibition PABPN1*	WT-PABPN1 Expression
6e10	88 %	91 %
1e10	63 %	13 %

BB-301: SCALABLE MANUFACTURING

50 Liter Reactor

- Produced with scalable baculovirus based methodologies and purification processes to control cost of goods.
- Using a modified AAV capsid for the generation of highly active BB-301 particles
- Benitec has developed a product specific process for producing high titer, highly pure BB-301:
  - Yields exceed 1e14 vector genomes/liter
  - Recovery yields in final product range from 30 – 40 %
- GMP grade clinical material produced at leading Contract Manufacturing Organization
- Currently manufacturing at 50L scale
- Clinical product to be generated at 250L scale

Silver stain of SDS protein gel
showing output of purification steps
(3 capsid bands expected in final product)

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