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

David Suhy / CSO

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This presentation contains "forward-looking statements" within the meaning of section 27A of the US Securities Act of 1933 and section 21E of the US Securities Exchange Act of 1934. Benitec has tried to identify such forward-looking statements by use of such words as "expects," "intends," "hopes," "anticipates," "believes," "could," "may," "evidences" and "estimates," and other similar expressions, but these words are not the exclusive means of identifying such statements. Such statements include, but are not limited to, any statements relating to Benitec's pipeline of ddRNAi-based therapeutics, including the initiation, progress and outcomes of clinical trials and any other statements that are not historical facts. Such forward-looking statements involve risks and uncertainties, including, but not limited to, risks and uncertainties relating to the difficulties or delays in our plans to develop and potentially 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 duration of our patent portfolio, the ability to procure additional sources of financing and other risks detailed from time to time in filings that Benitec makes with US Securities and Exchange Commission, including our most recent annual report on Form 20-F and our reports on Form 6-K. Such statements are based on management's current expectations, but actual results may differ materially due to various factors, including those risks and uncertainties mentioned or referred to in this presentation. Accordingly, you should not rely on those forward-looking statements as a prediction of actual future results.

Pipeline Programs

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Program	Delivery	Discovery	Preclinical	IND-Enabling	Phase I/II	Status
Oncology						
HNSCC - BB-401	Plasmid intratumoral					• Phase 1 clinical POC complete • Phase 2 FPE – 1Q18
HNSCC - BB-501	ddRNAi intratumoral					• Construct design complete • *In vivo* proof of concept – 4Q17
Infectious Disease						
HBV - BB-103	AAV intravenous					• Pre-IND completed • IND-enabling work ongoing
Ocular Disease						
AMD - BB-201	Novel AAV intravitreal					• Capsid biodistribution complete • *In vivo* proof of concept – 4Q17
Orphan Disease						
OPMD - BB-301	AAV intramuscular					• *In vivo* proof of concept – 3Q17

Benitec Technology: DNA-Directed RNAi (ddRNAi)

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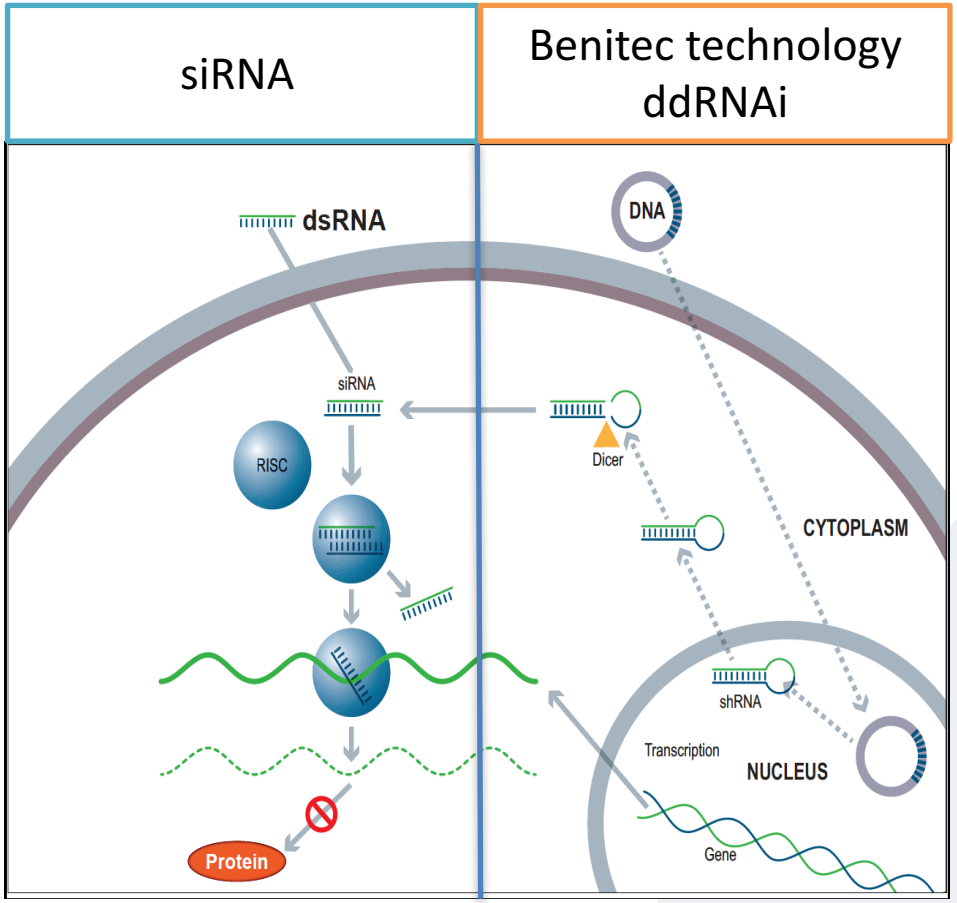
- Combines RNA interference with gene therapy delivery
- Long term therapeutic potential from a single administration
- Steady state levels of gene expression
- Silence a single gene or target multiple genes simultaneously
- Silence/replace strategies of mutant proteins



ddRNAi Platform: Flexibility in shRNA Expression Design to Fit Disease Indication

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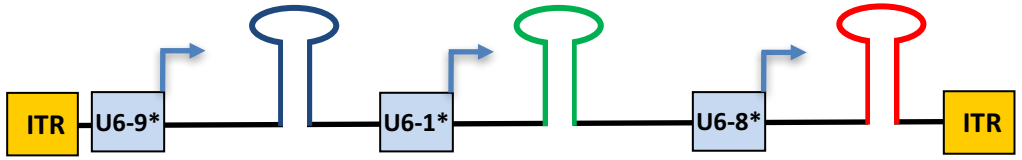
Characteristics:

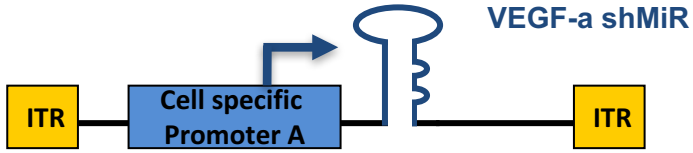
- Multi-targeting
- Lowered shRNA expression through altered promoters



Drug:

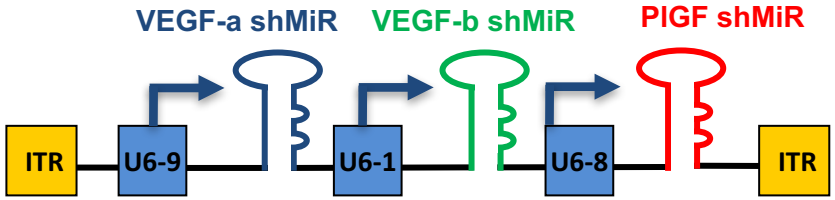
TT-034 (HCV)

- Tissue restricted expression
- Defined shRNA loop processing



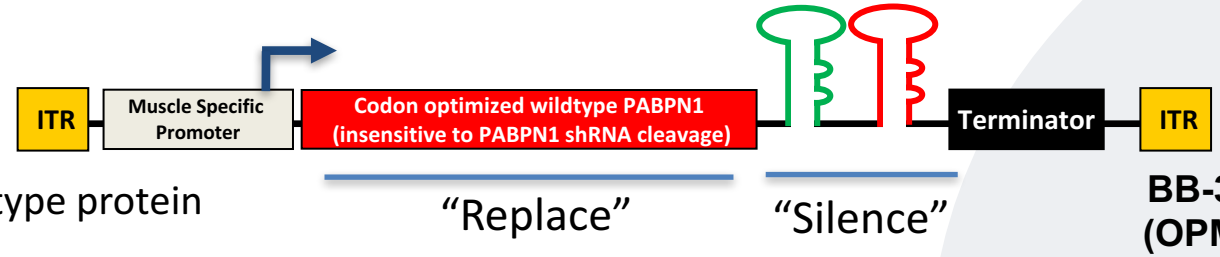
BB-AMD-211 (Ocular)

- Multi-targeting
- Defined shRNA loop processing
- More Robust shRNA expression



BB-201 (Ocular)

- Tissue restricted expression
- Silence disease causing allele
- Replace expression with wildtype protein



BB-301 (OPMD)

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OPMD

Oculopharyngeal Muscular Dystrophy

Clinical Features of OPMD

Rare autosomal dominant inheritance

- 1:100,000 (Europe)
- As high as 1:600 in specific populations
- Founder effect in Quebec, Canada

Typically onset occurs in the fifth to early sixth decade of life

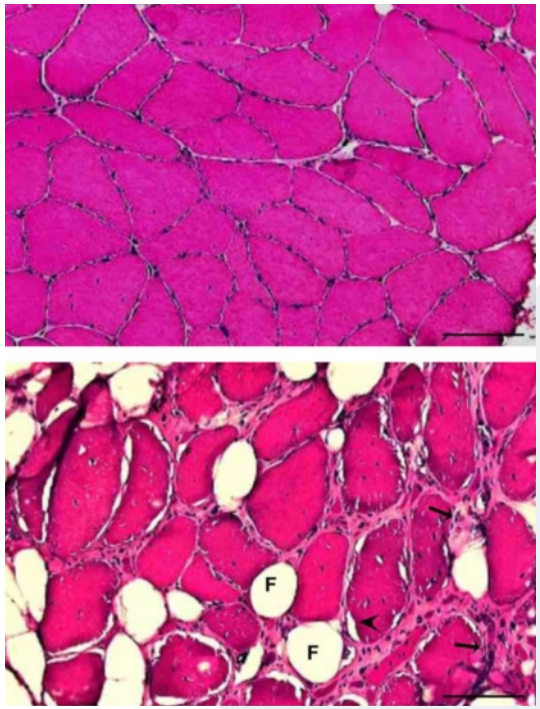
Characterised by:

- eyelid drooping (ptosis)
- swallowing difficulty (dysphagia)
- proximal limb weakness
- death due to aspiration pneumonia & malnutrition

Histopathology

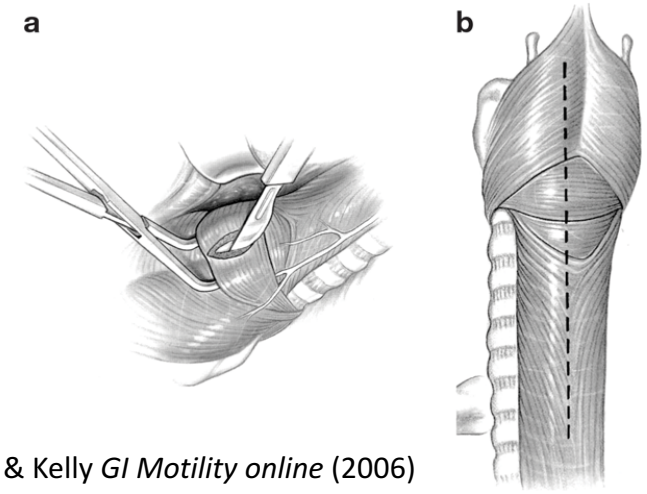
- Decrease of muscle fiber number
- Variation in the size of muscle fibers
- Fibrosis (connective tissue)

Raz et al., *BMC Neurology* 2013, **13**:70



Only Widely Used Treatment is a Surgical Procedure That is Ineffective Over Time

- **Cricopharyngeal myotomy :** a surgical intervention to improve swallowing, but does not correct the progression of the disease since it has a genetic basis.



Chu & Kelly *GI Motility online* (2006)

- **Stem cell transplants**: grafting of autologous myoblasts isolated from unaffected quadriceps or sternocleidomastoid muscles into the esophagus of the patient. Some short term efficacy but transplanted cells still carry the genetic defect.

Molecular Therapy (2014); **22** 1, 219–225

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

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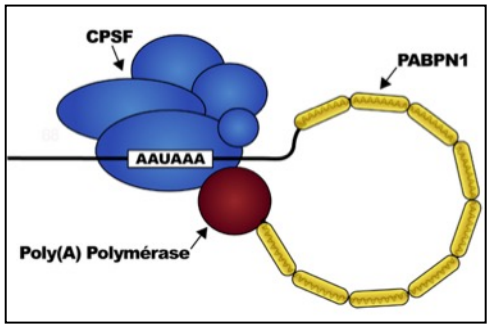
PABPN1:

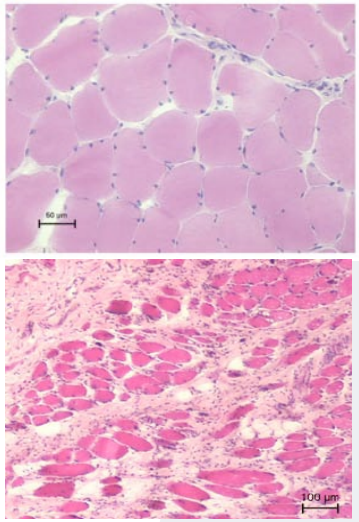
- a ubiquitous factor that promotes interaction between the poly(A) polymerase and CPSF (cleavage and polyadenylation specificity factor) and thus controls the length of mRNA poly(A) tails, mRNA export from the nucleus, and alternative poly(A) site usage.



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



Non-affected

Affected

Intranuclear Inclusions (INIs), the Hallmark of OPMD

Expansion of the short (GCG) trinucleotide repeat in the coding sequence of PABPN1

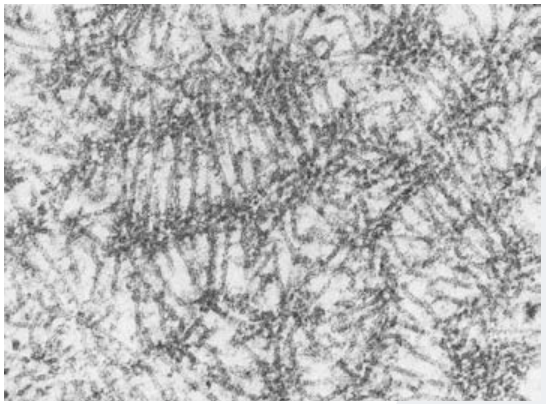
↓

The mutated protein has 11-17 alanines in the N-Terminal domain instead of 10

↓

Protein aggregation forms intranuclear inclusions (INIs)

- Tubular filaments
- Resistant to degradation
- INIs found in the nuclei of skeletal muscle fibres (both affected and non-affected)



Tomé & Fardeau, 1980

Other Experimental Therapies in Development

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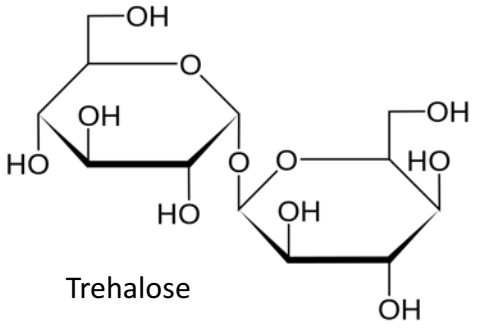
Trehalose

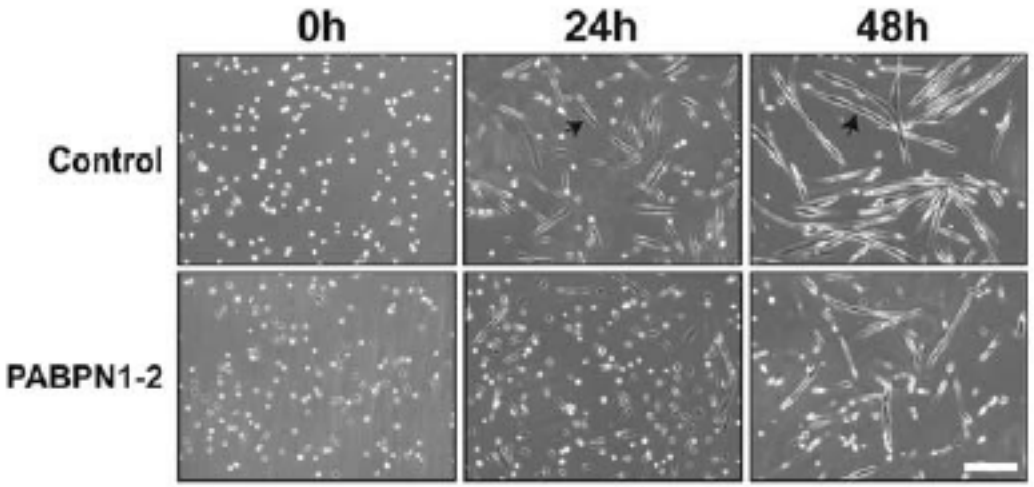
- BioBlast is in Phase II clinical testing of Cabaletta, a chemical chaperone that prevents pathological aggregation of proteins within cells. The active ingredient Trehalose, a disaccharide of glucose, is thought to induce autophagy and stimulate intracellular clearance of the protein aggregates.

- The drug is administered weekly by intravenous infusion.



Trehalose

PABPN1 is Required to Maintain Muscle Function



Human Molecular Genetics, 2010, Vol. 19, No. 6 **1058–1065**
doi:10.1093/hmg/ddp569
Advance Access published on December 24, 2009

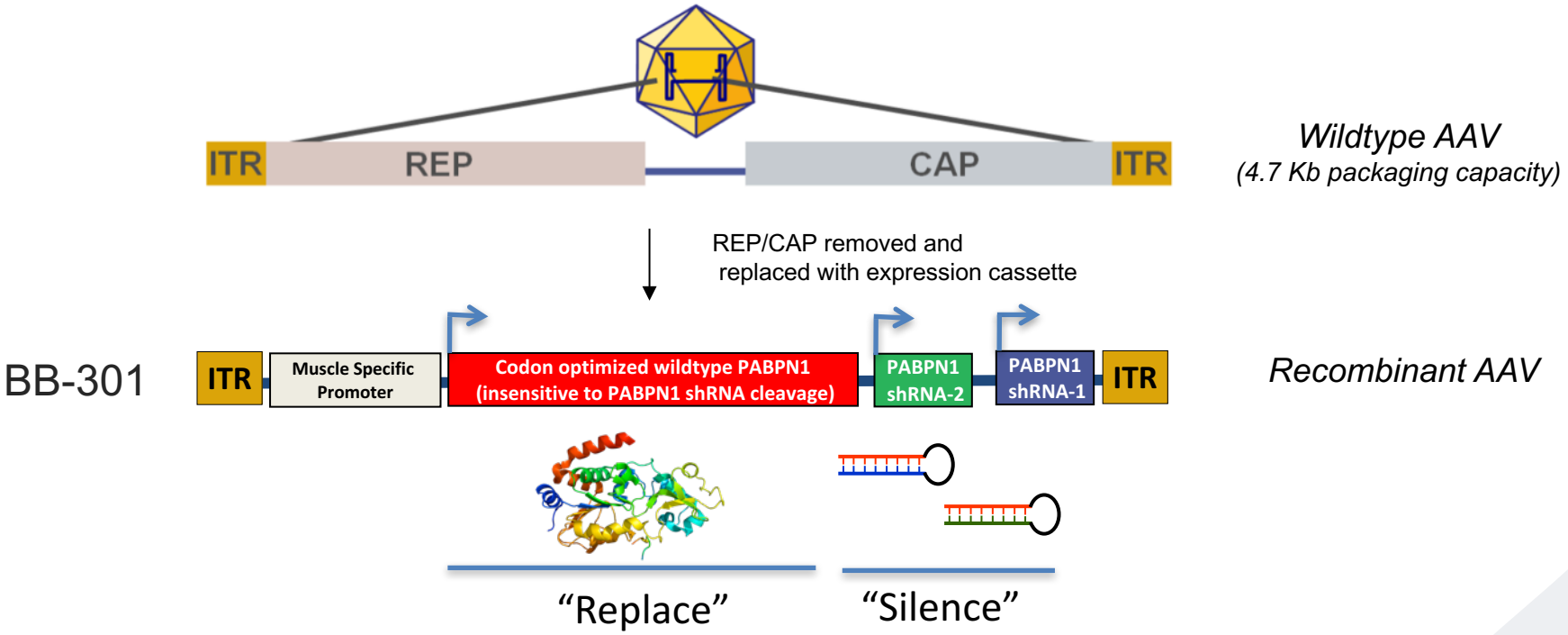
Loss of nuclear poly(A)-binding protein 1 causes defects in myogenesis and mRNA biogenesis

Luciano H. Apponi[1], Sara W. Leung[2], Kathryn R. Williams[1], Sandro R. Valentini[3], Anita H. Corbett[2,*] and Grace K. Pavlath[1,*]

- PABPN1 is required for normal myoblast proliferation and differentiation
- PABPN1 is required for proper polyadenylation in muscle cells
- PABPN1 is required for proper poly(A) RNA export from the nucleus

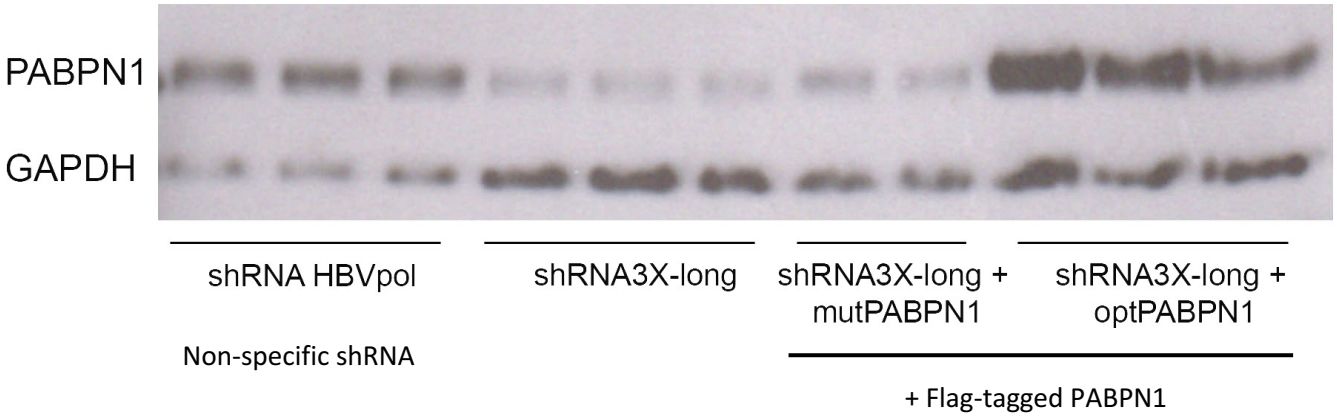
****Thus, an effective treatment likely requires maintaining endogenous function in addition to eliminating mutant protein aggregates**

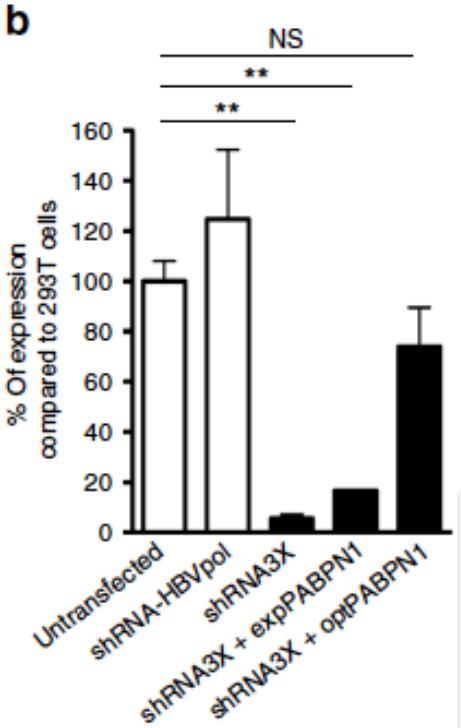
BB-301: 'Silence and Replace' Approach



- Non-integrating, non-pathogenic viral delivery system
- To date, AAV has been used in over 173 clinical trials with excellent safety record
- Sustained expression (years) following single injection

Expression of “codon optimized” wildtype PABPN1 is not knocked down by shRNA



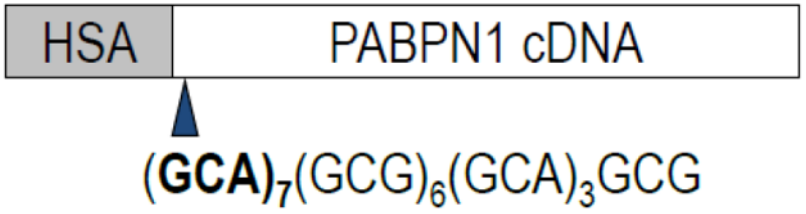


Initial sequence GGACATGGA GGAA GAA GC TGAGAAGCTAA AGGAG CTAC...

Codon-modified GGACATGGAAGAGGAGGCCGAAAAACTAACGGAGTTAC...

**Codon modified wildtype PABPN1 is resistant to knockdown with shRNA

An Animal 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

Nature Medicine **11**, 672 - 677 (2005)
Published online: 1 May 2005 | doi:10.1038/nm1242

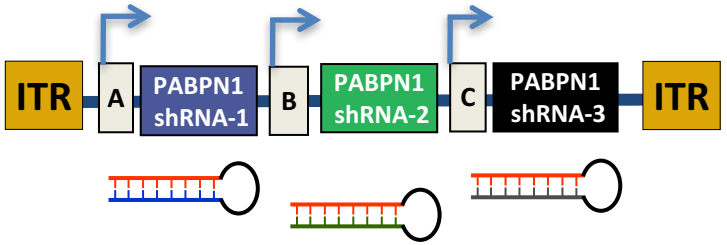
Doxycycline attenuates and delays toxicity of the oculopharyngeal muscular dystrophy mutation in transgenic mice

Janet E Davies[1], Lin Wang[1], Lourdes Garcia-Oroz[1], Lynnette J Cook[1], Coralie Vacher[1], Dominic G O'Donovan[2] & David C Rubinsztein[1]

Assessment of Efficacy in the A17 Mouse Model

Mice TA Muscles injected with:

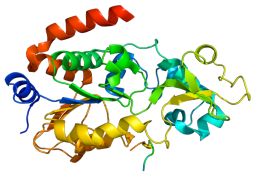
2.5e10 vg scAAV8-shRNA3X
1.3e11 vg ssAAV9-optPABN1
Analyses at week 18 post injection



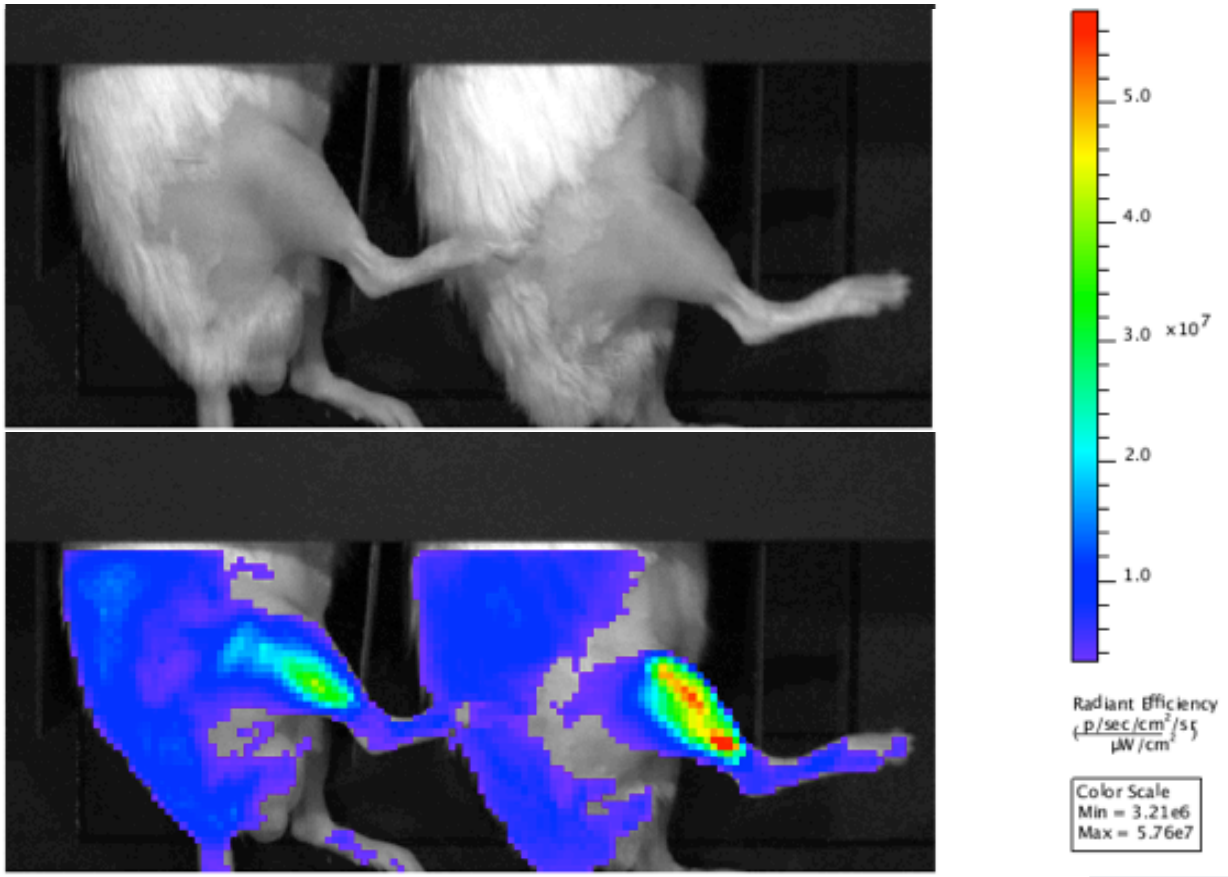
shRNA3x

AND / OR

optPABPN1



Use of AAV / Intramuscular Injections for Delivery into Muscles Tissues



Assessments

- Intranuclear Inclusions
- Fibrosis
- Muscle Fiber Size
- Muscle Strength
- Gene Expression

Silence and Replace Strategy Reduces Insoluble Aggregates in Muscle Sections of Treated A17 Mice

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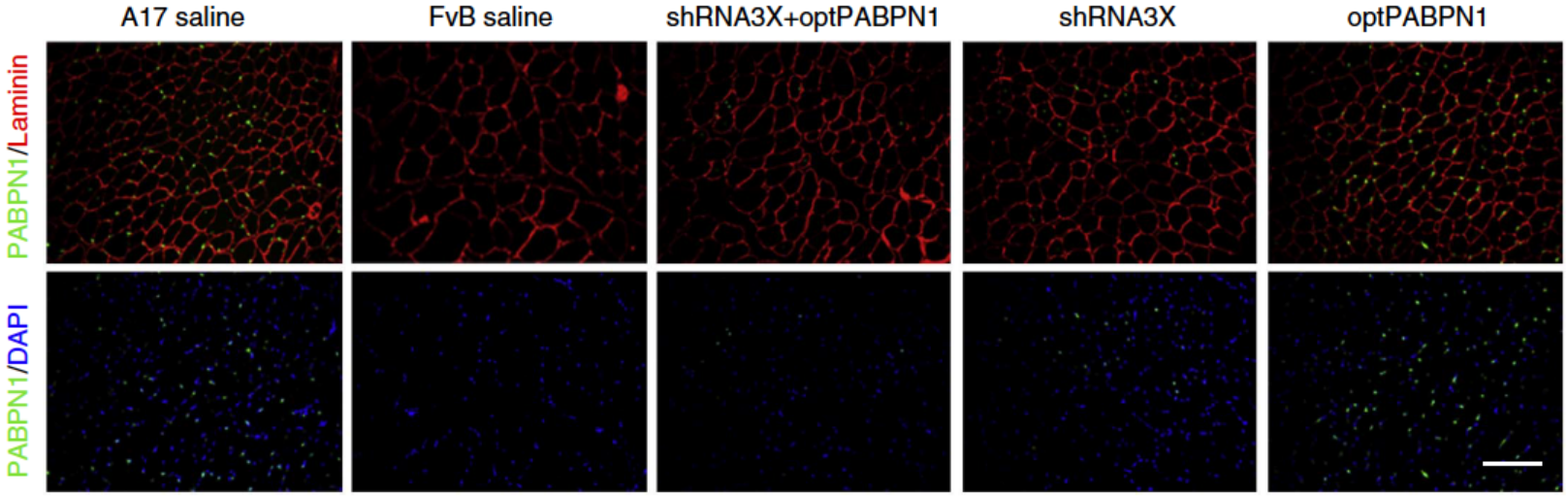

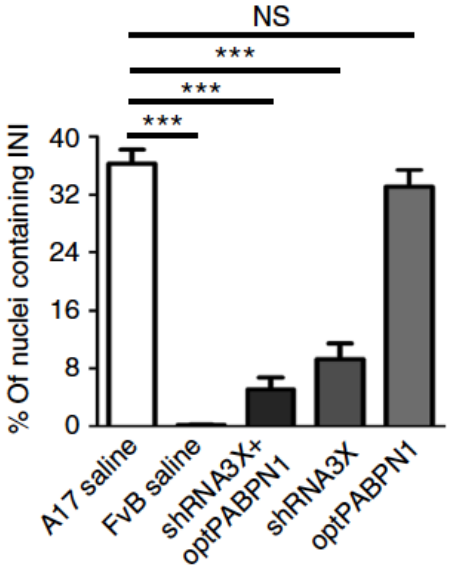

Silence and Replace Strategy Reduces Fibrosis in Transverse Muscle Sections of Treated A17 Mice

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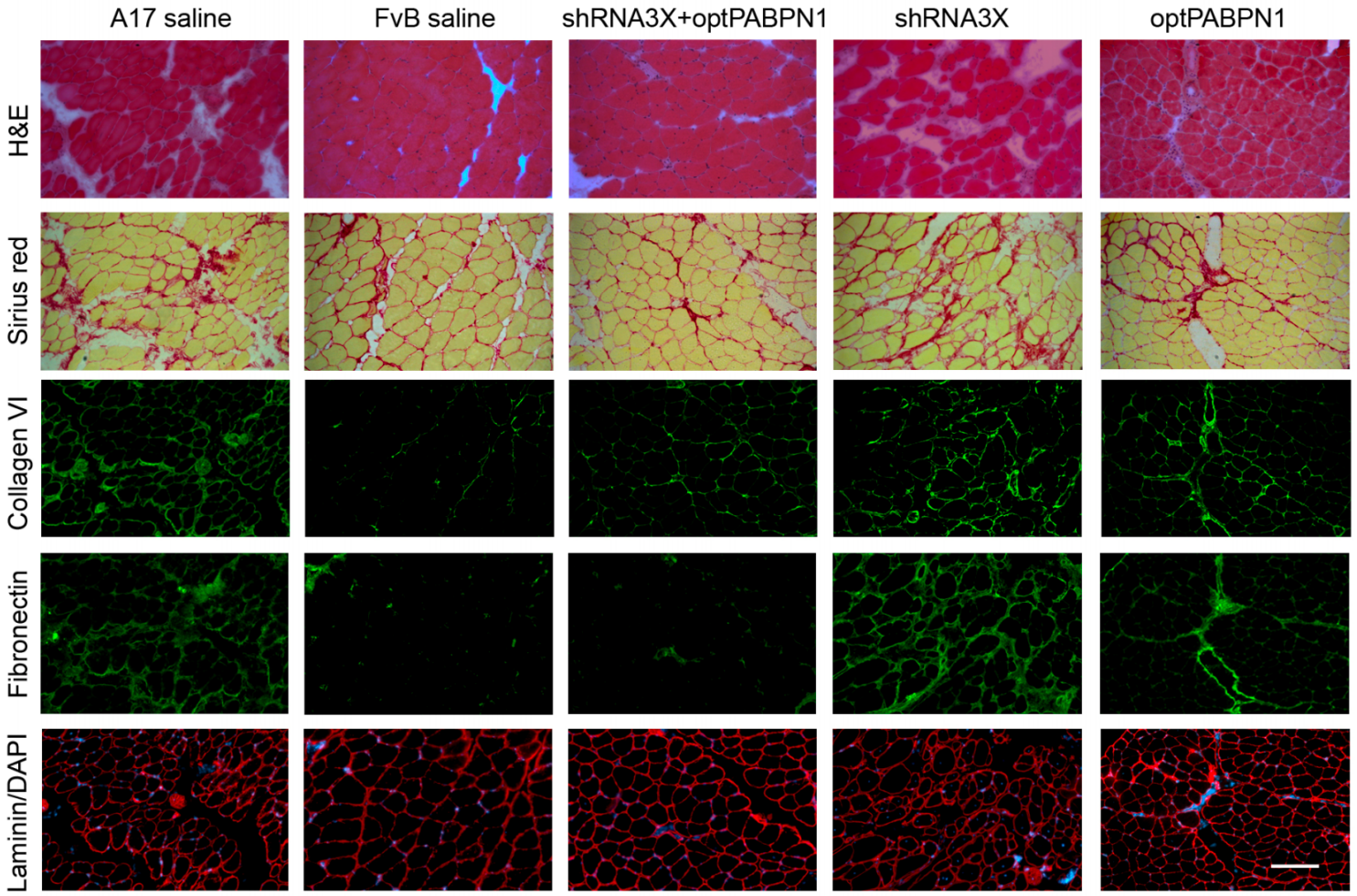

Partial Reversal of Atrophy: a Cross Section Analysis of Muscle Fibers in Treated A17 Mice

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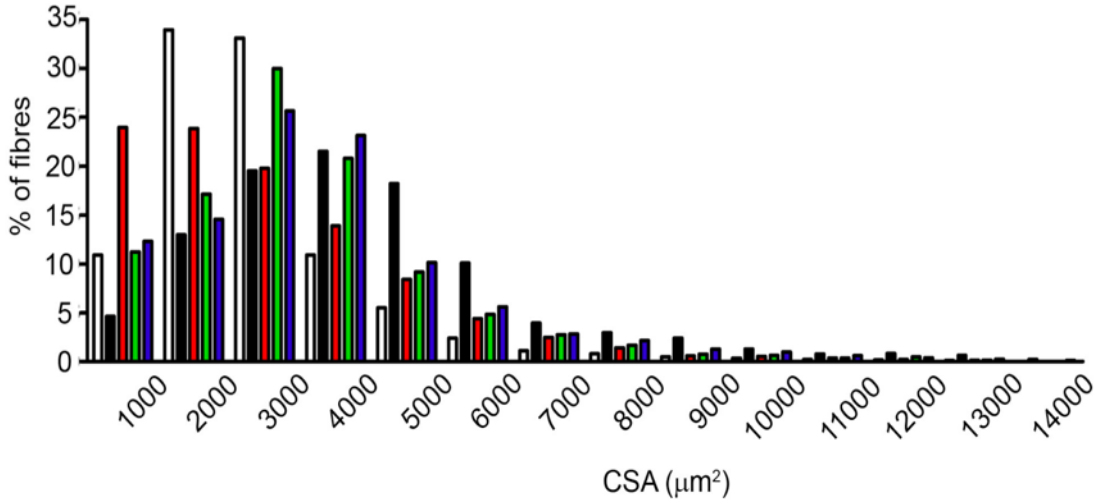
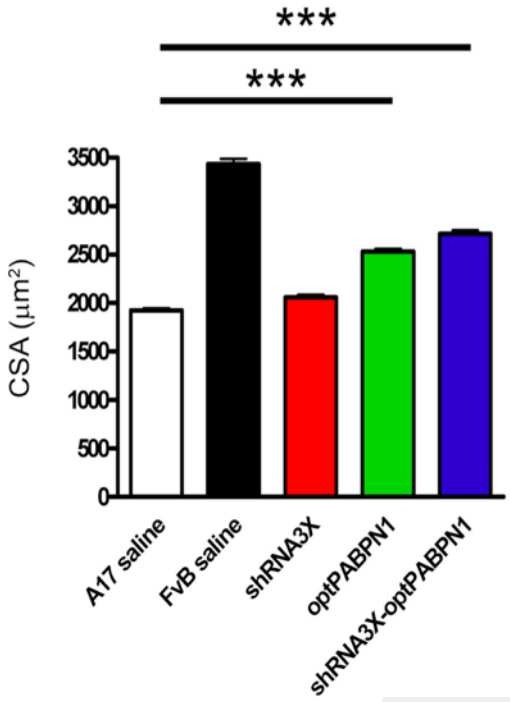
muscle fiber size assessed by quantifying fiber cross-sectional area (CSA)





Assessment of Muscle Atrophy and Restoration of Specific Force in Treated A17 Mice

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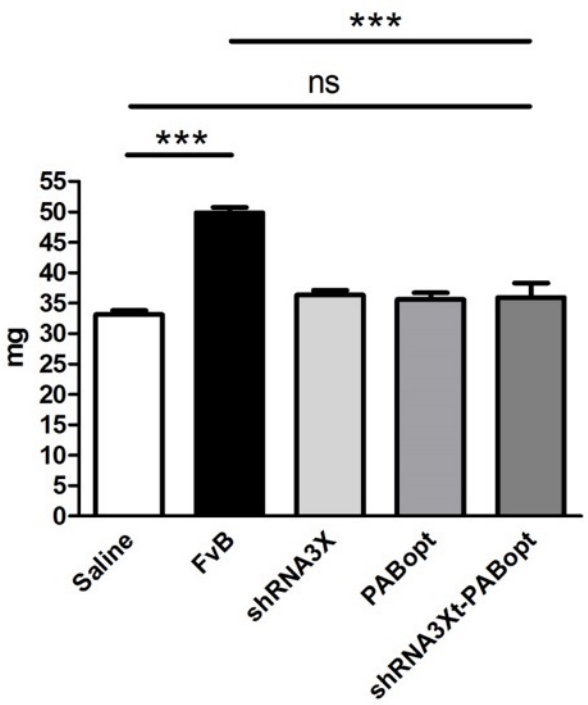
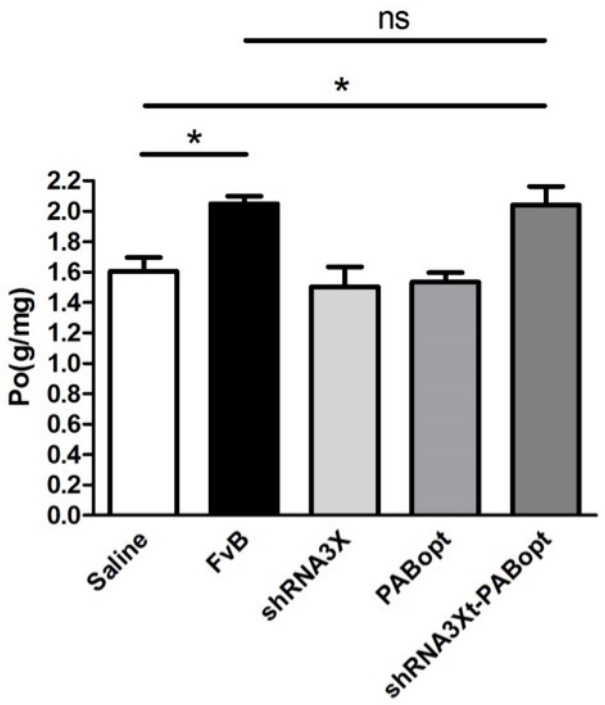
Muscle weight



Reduced Fibrosis +
Partial Reversal of Atrophy

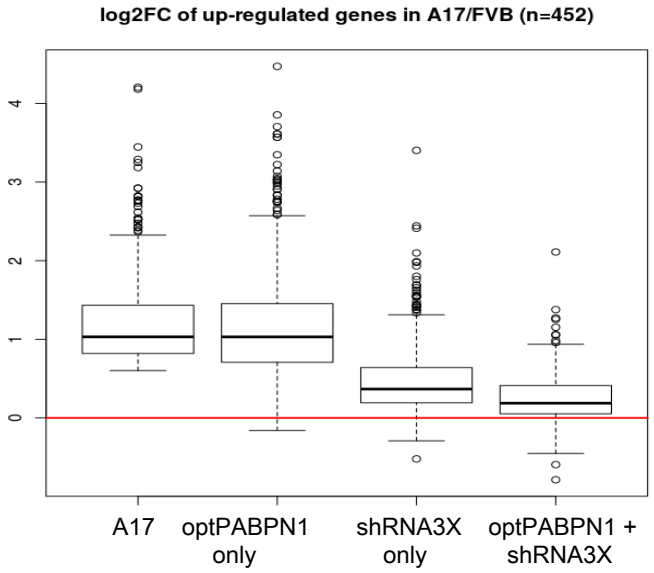
Specific Force

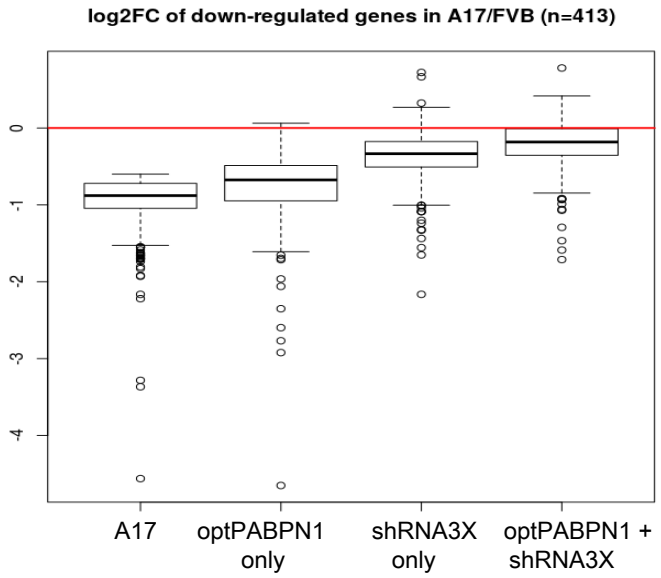


Specific force calculated by normalizing maximal force for muscle weight

Impact of Treatment of A17 Mice: a Microarray Analyses

- expPABPN1 expression in A17 mice causes extensive remodelling of muscle transcriptome
  *(*Trollet et al. *HMG* 2010*;* Anvar et al. *Sk Muscle* 2011; Chartier et al*. Plos Genet* 2015)
- Transcriptome analyzed from current experiment





- In A17 mice vs wildtype, 865 transcripts were deregulated FC>2; p<0.05
- Dual treatment with shRNA3X + optPABPN1 results in only 12 genes deregulated, a 98% “correction”

OPMD Program Highlights

- ddRNAI constructs design highlights unique ‘silence and replace’ therapeutic strategy for monogenic disease
- Neither overexpression of wildtype protein or knockdown on disease protein impacts disease. Only a combined approach efficiently restores function.
- A single vector approach simplifies the CMC approach for clinical materials
- Continuing to characterize *in vivo* efficacy of clinical candidates

- Orphan Drug Designation granted from the EU January 2017

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