



NASDAQ: BNTC  
ASX: BLT

## Cell & Gene Meeting on the Mesa

David Suhy  
Chief Scientific Officer

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# Business Overview

A multi-product clinical stage company in 2018



*Benitec has created a novel combination of gene therapy and RNA interference (gene silencing) to change treatment paradigms of human disease*

## PROVEN TECHNOLOGY

Validated technology with two clinical assets by the end of 2018

## ROBUST PIPELINE

Assets in oncology, orphan genetic disorders, retinal disease, and infectious disease

## VALUABLE PRODUCTS

Human therapeutic products for commercialization, partnering, and collaborations

# Experienced Executive Team

<b>Greg West</b> Chief Executive Officer	<ul style="list-style-type: none"><li>• Former CFO of Benitec Biopharma, 10 years biotech experience</li><li>• Prior roles at PriceWaterhouse, Bankers Trust, Deutsche Bank and NZI</li></ul>
<b>Dr. David Suhy</b> Chief Scientific Officer	<ul style="list-style-type: none"><li>• Former SVP of Research &amp; Development, Benitec Biopharma</li><li>• Prior roles at Tacere Therapeutics, Antara Biosciences and PPD Discovery</li></ul>
<b>Georgina Kilfoil</b> Chief Clinical and Development Operations Officer	<ul style="list-style-type: none"><li>• Former VP of Clinical Operations, Benitec Biopharma</li><li>• Prior roles at Anthera Pharmaceuticals, InClin and Peninsula Pharmaceuticals</li></ul>
<b>Dr. Cliff Holloway</b> Chief Business and Operating Officer	<ul style="list-style-type: none"><li>• Former CEO and MD of Sienna Cancer Diagnostics, and Biosceptre International</li><li>• Prior VP BD role at Arana Therapeutics (now Teva Pharma)</li></ul>
<b>Bryan Dulhunty</b> Chief Financial Officer	<ul style="list-style-type: none"><li>• Former Executive Chairman, Viralytics</li><li>• Prior roles as NED, MD, CFO and Company Secretary of a number of listed and non-listed biotech companies</li></ul>
<b>Dr. Michael Graham</b> Head of Discovery & Founding Scientist	<ul style="list-style-type: none"><li>• Discoverer of ddRNAi at CSIRO; Former Senior Research Fellow, University of Queensland</li><li>• Prior roles at QDPI and CSIRO</li></ul>

## Programs advancing to the clinic

- Phase II ready EGFR-targeted gene silencing therapeutic achieved POC in **head & neck cancer** entering confirmatory Phase II trial in Q1 2018.
- Unique “silence and replace” therapeutic against orphan disease **oculopharyngeal muscular dystrophy** by silencing expression of the mutant disease-causing gene (PABPN1) and simultaneously reintroduces a normal copy of the gene. Anticipated to enter clinic at end of 2018.
- Other programs targeting **retinal disorders** and **infectious disease** expected to be clinic-ready late 2018/2019.

## Capital markets access

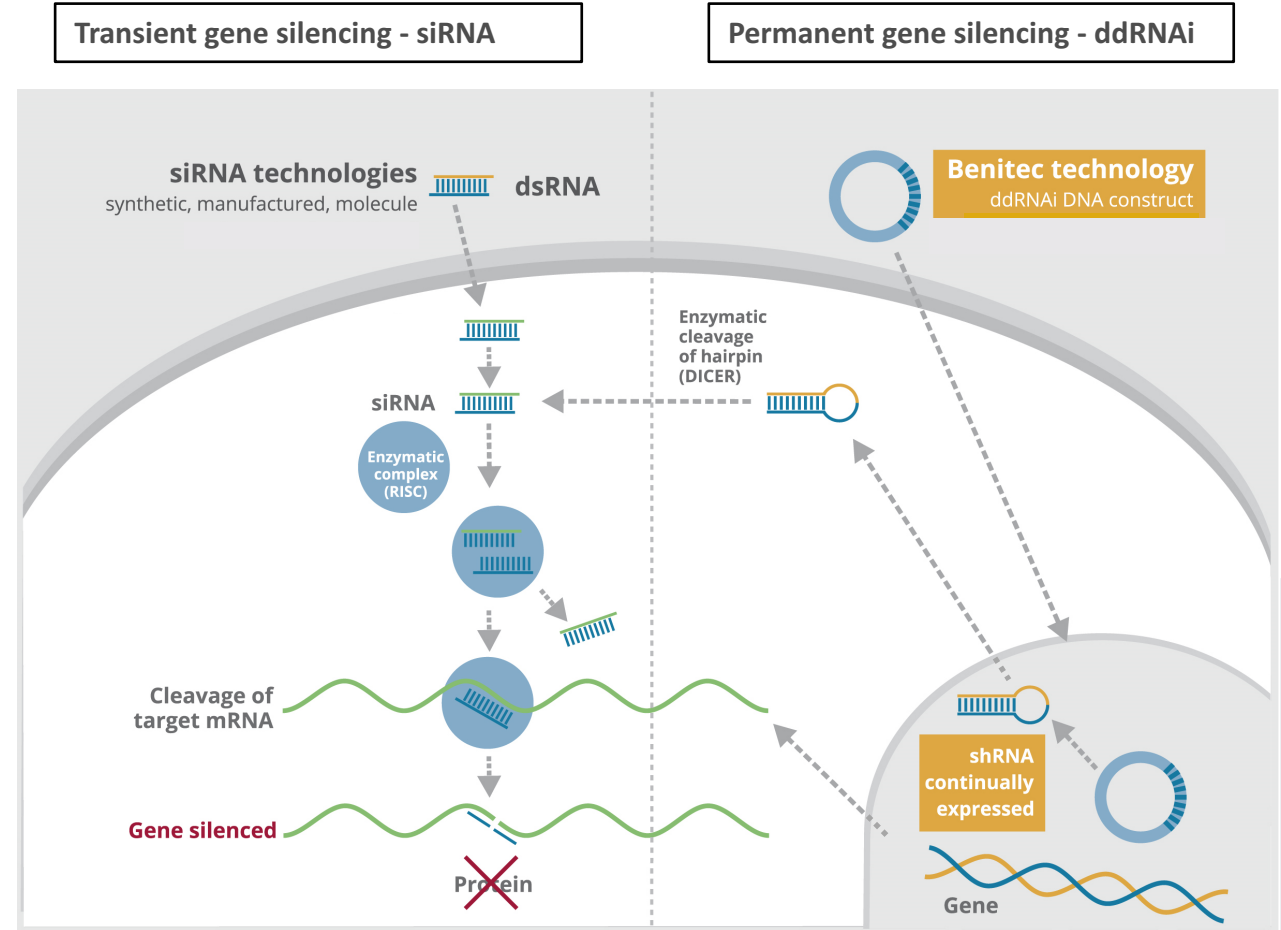
- Listed on ASX (2002) and NASDAQ (2015)
- Has raised US\$40M capital since 2014
- US SEC shelf registration June 2017

## Strong in-house capabilities

- 23 staff with scientific operations in Hayward CA, including 13 PhDs with deep expertise in gene therapy
- In-house manufacturing expertise for process optimization and scalability
- Extensive commercial and drug development expertise

# Permanent Gene Silencing with 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 simultaneously target multiple genes
- “Silence and Replace”: Simultaneous silencing of disease causing genes with co-expression of normal genes to restore function



# Benitec Pipeline Programs

Program	Delivery	Discovery	Preclinical	IND-Enabling	Early stage clinical (IND – Phase 2)	Late stage clinical (Phase 2 – Phase 3)	Commercial Rights
Oncology – head and neck squamous cell carcinoma (HNSCC)							
HNSCC BB-401	Plasmid Intratumoral						• global
HNSCC BB-501	ddRNAi Intratumoral						• global
Orphan Disease – oculopharyngeal muscular dystrophy (OPMD)							
OPMD BB-301	AAV Intramuscular						• global
Retinal Disease – age-related macular degeneration (AMD)							
AMD BB-201	Novel AAV Intravitreal						• global
Infectious Disease – hepatitis B (HBV)							
HBV BB-103	AAV Intravenous						• global

# Head and Neck Squamous Cell Carcinoma (HNSCC) Program Update

Program	Delivery	Discovery	Preclinical	IND-Enabling	Early stage clinical (IND – Phase 2)	Late stage clinical (Phase 2 – Phase 3)	Commercial Rights
Oncology – head and neck squamous cell carcinoma (HNSCC)							
HNSCC BB-401	Plasmid Intratumoral	<div></div>					<ul style="list-style-type: none"><li>global</li></ul>
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# Head and Neck Squamous Cell Carcinoma (HNSCC)

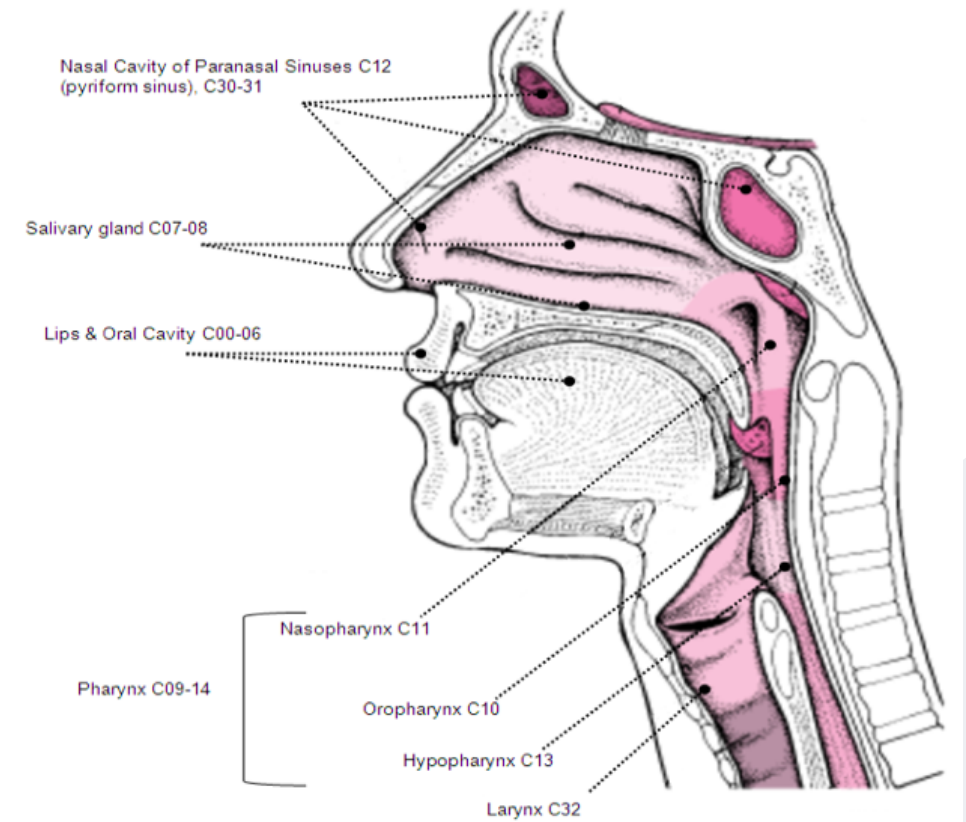
## Incidence and Patient Mortality:

- Circa 64,000 patients diagnosed annually in US
- 50% of patients expected to develop recurrent or metastatic disease
- 13,000 deaths annually in the US
- ***Over 90% of HNSCC lesions overexpress epidermal growth factor receptor (EGFR)***

## Unmet Medical Need:

- Significant patient morbidity derived from loco-regional tumor growth and progression in confines of small anatomical space
- Durable tumor reduction or eradication
- Lack of biomarkers to reliably predict response to targeted therapy

## Anatomical sites of HNSCC

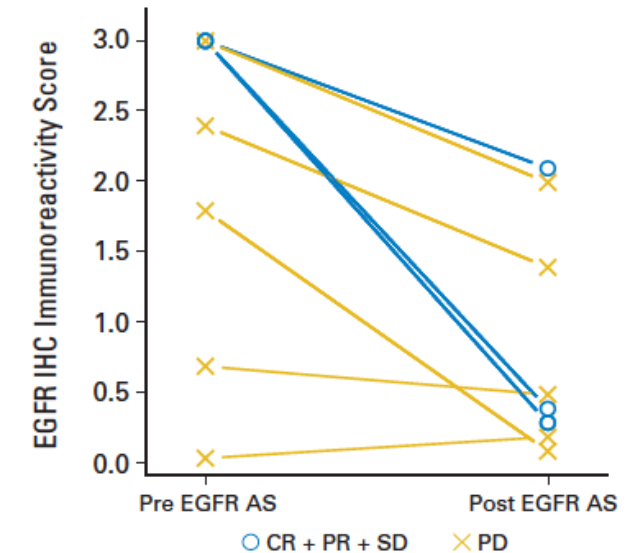
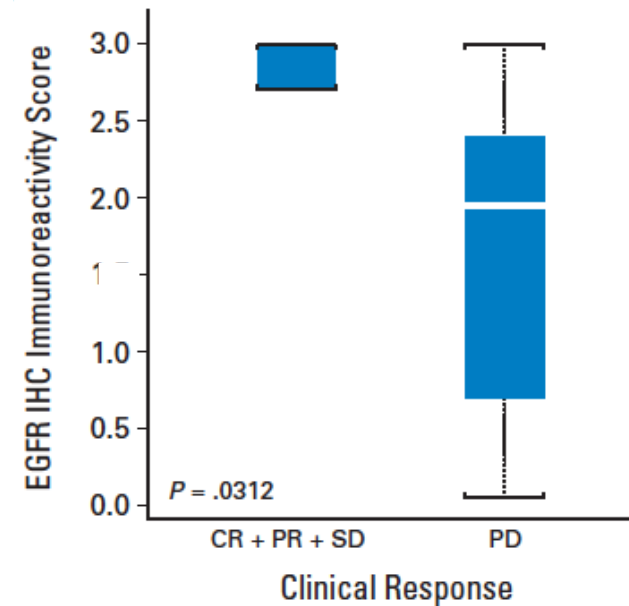


# BB-401: Expressed Anti-Sense RNA Against EGFR

## Phase 1 Single Agent Clinical Data

- Phase I study\* of 17 patients with advanced, refractory HNSCC
- Safety and efficacy evaluated following direct intra-tumoral injection weekly for 4 weeks:
  - 29 % (5 patients) -Objective Response
  - Of these 2 patients experienced Complete Response (100% reduction in size by RECIST) & 3 patients Partial Responses (reduction >30% by RECIST)
  - 2 additional patients - Stable Disease
  - 41% overall disease control rate
  - 6.5 months observed anti-tumor response

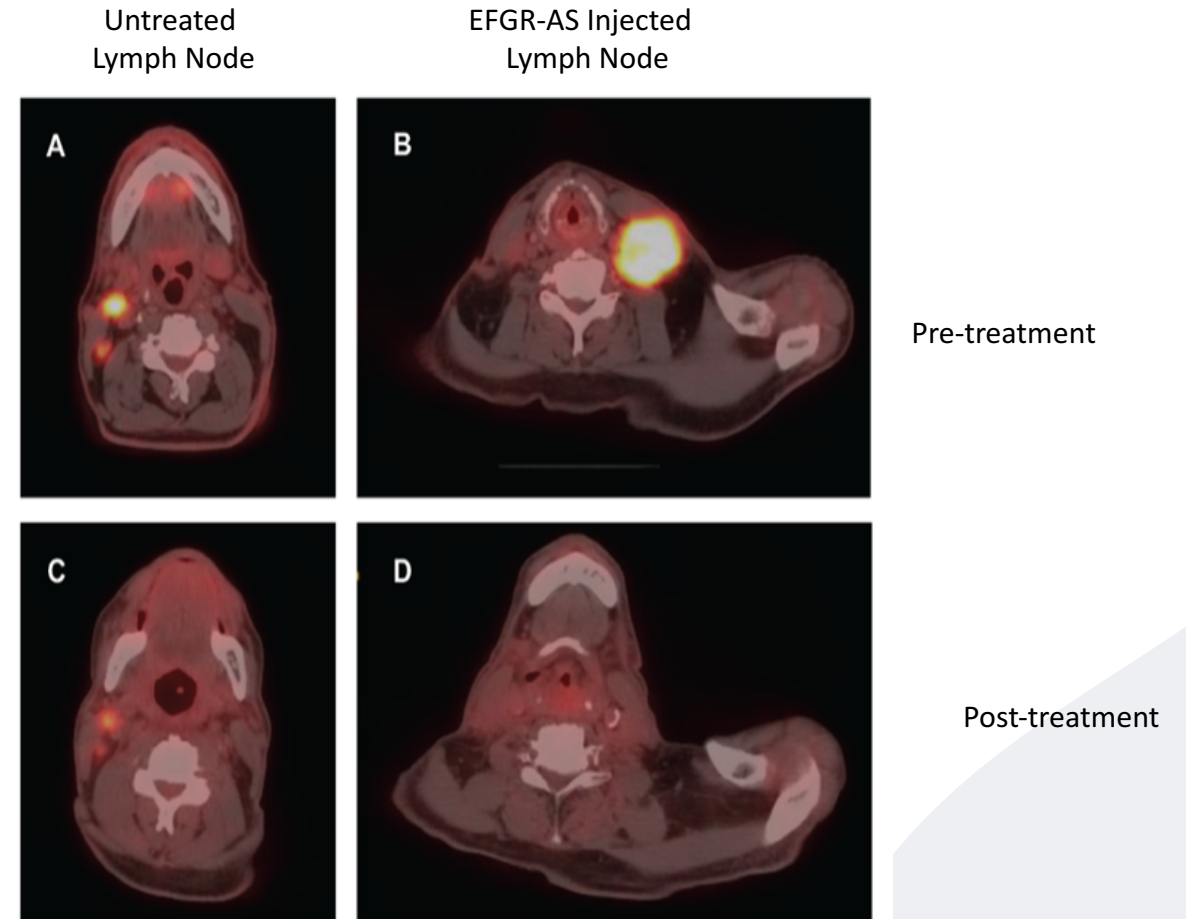
- Strong correlation between baseline level of EGFR expression and clinical response



\*Lai *et al.*, Journal of Clinical Oncology, 2009

# BB-401: Follow on Phase 1 Study of BB-401 in Combination with Cetuximab and Radiation

- 6 patients were treated in a Phase 1 study of BB-401 in combination with radiation and cetuximab
- 5 of 6 patients experiencing Objective Responses (83%)
- 4 patients Complete Response & 1 patient Partial Response



Grandis et al, University of Pittsburgh  
Poster from ASCO 2015

# Head & Neck Squamous Cell Carcinoma

## Clinical Candidate BB-401: Product Overview

### Head & Neck Squamous Cell Carcinoma

- Over 50,000 new cases diagnosed in US in 2017, global market estimated at US\$1.5 billion in 2024
- Morbidity caused by spatial effects of tumors in confined anatomical structures of the head and neck
- Over 90% of HNSCC overexpress epidermal growth factor receptor (EGFR)

### BB-401 Product Profile

- EGFR Targeted via expressed antisense RNA EGFR
- In Phase I, strong correlation of response versus EGFR expression
- Robust response when compared to other monotherapy treatments or when paired with SOC

### Value / Commercial Opportunity

- Near-term value inflection point: Phase II study in up to 50 patients planned for initiation in 1Q18
- Selective and direct targeting of malignant lesions underlying the core morbidity could uniquely address the unmet medical need in HNSCC
- BB-401 is intended to be paired with diagnostic

# Oculopharyngeal Muscular Dystrophy (OPMD) Program Update

Program	Delivery	Discovery	Preclinical	IND-Enabling	Early stage clinical (IND – Phase 2)	Late stage clinical (Phase 2 – Phase 3)	Commercial Rights
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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:

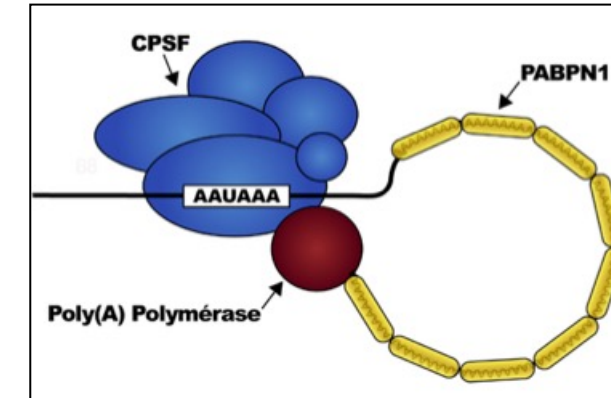
- Decrease of muscle fiber number
- Variation in the size of muscle fibers
- Fibrosis (connective tissue)



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

## PABPN1:

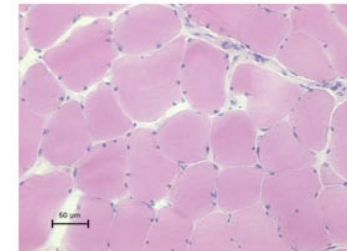
- A ubiquitous factor that promotes interaction between the poly(A) polymerase and CPSF (cleavage and polyadenylation specificity factor) and thus controls the length of mRNA poly(A) tails, mRNA export from the nucleus, and alternative poly(A) site usage.



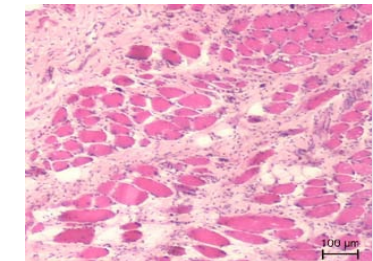
## In OPMD:

- 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) <sub>6</sub>	-----	(GCA) <sub>3</sub>	GCG GGG GCT GCG..
MUT	ATG (GCG) <sub>6</sub>	(GCG) <sub>1-7</sub>	(GCA) <sub>3</sub>	GCG GGG GCT GCG...--

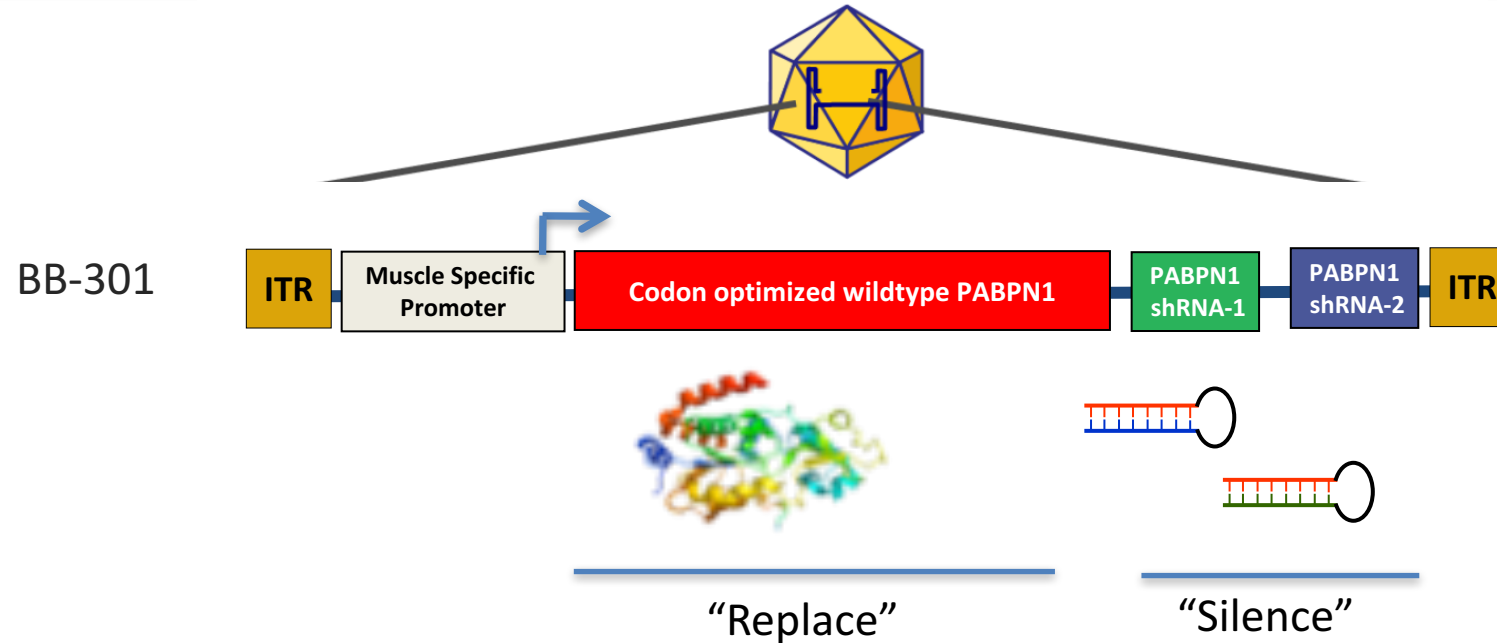


Non-affected



Affected

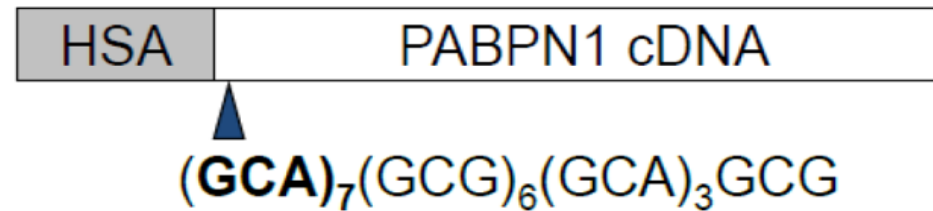
# BB-301: 'Silence and Replace' Approach



	G	S	G	P	G	R	R	R	H	L	V	P	G	A	G	G	E
Wild type Sequence	ggctccggggccggggcgggcggcgccatcttgtgcccggggccggtggggag																
Codon Optimized Sequence	ggc	AG	cgg	Ccc	Tgg	CAG	Acg	gcg	Gcat	cT	Ggt	Ccc	Tgg	Cg	ccg	A	ggggag
	G	S	G	P	G	R	R	R	H	L	V	P	G	A	G	G	E

← Insensitive to shRNA

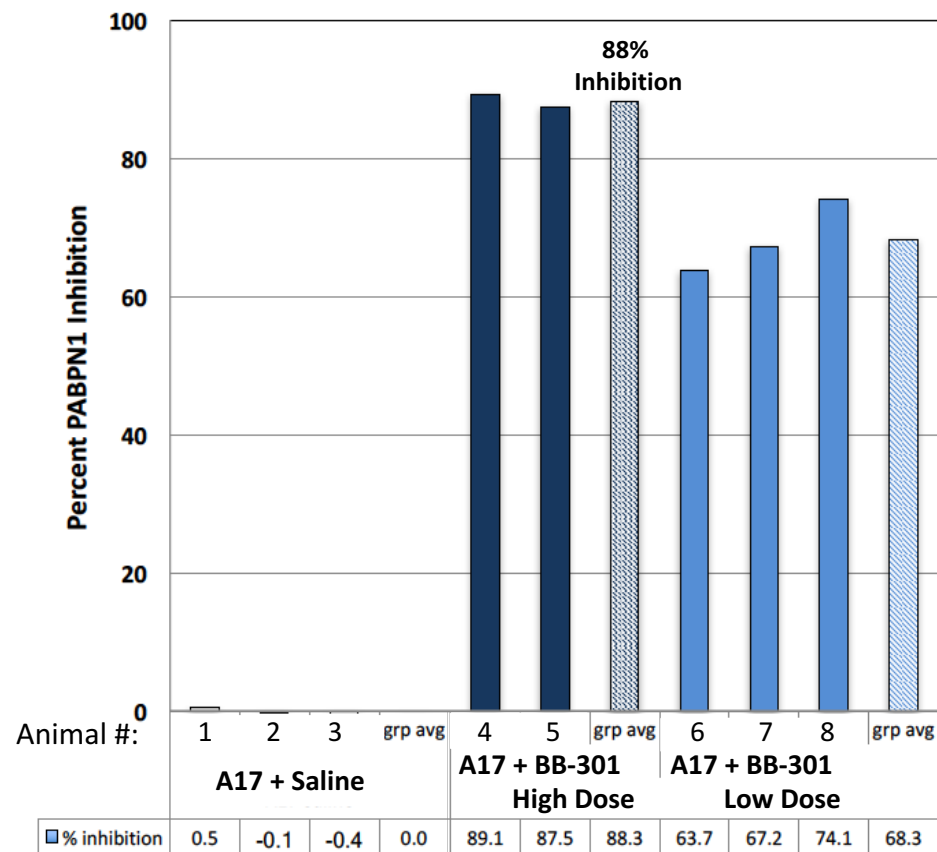




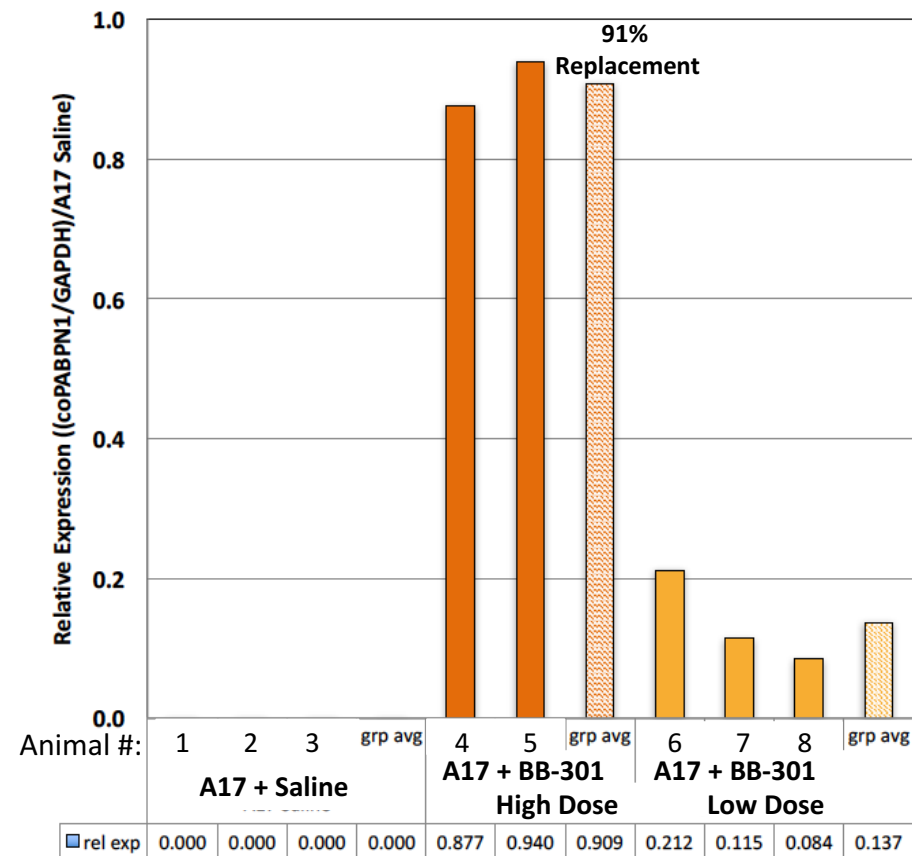
- Transgenic mouse: express a mutated bovine PABPN1 driven by the human skeletal actin promoter in addition to the endogenous PABPN1
- Recapitulates severe muscle atrophy
- Mimics many of the disease pathologies:
  - Progressive muscle weakness/ atrophy
  - Fibrosis
  - Mitochondrial / Ubiquitin-Proteasome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

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

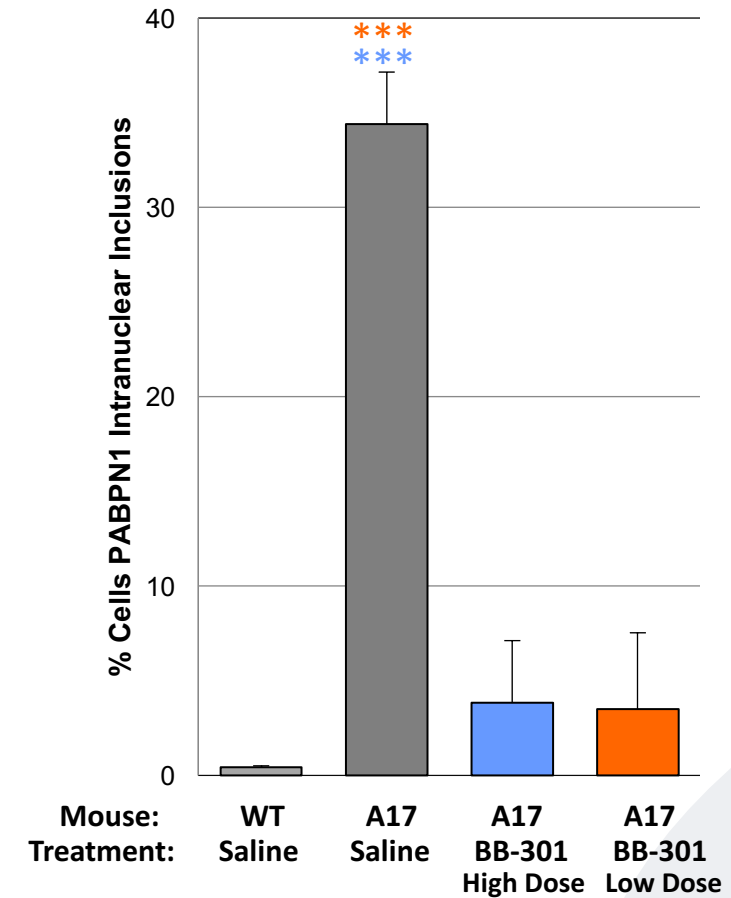
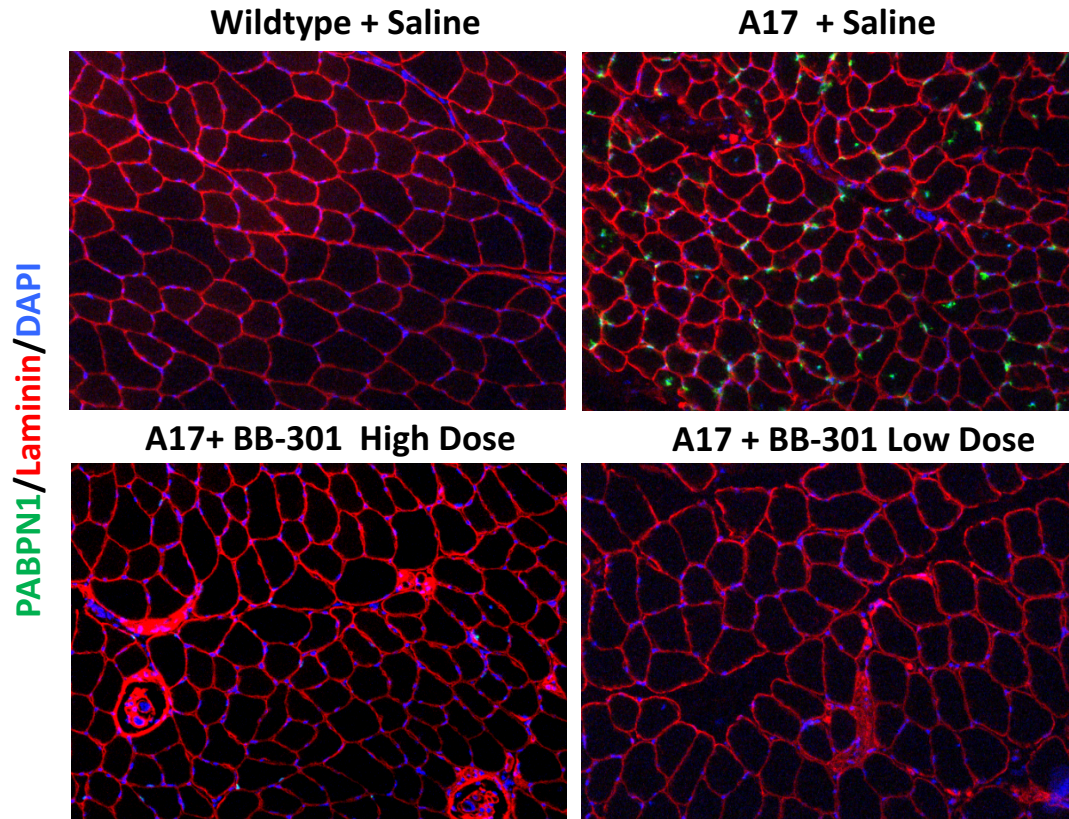
**SILENCE: Inhibition of PABPN1 Expression**



**REPLACE: Codon-Optimized PABPN1 Expression**

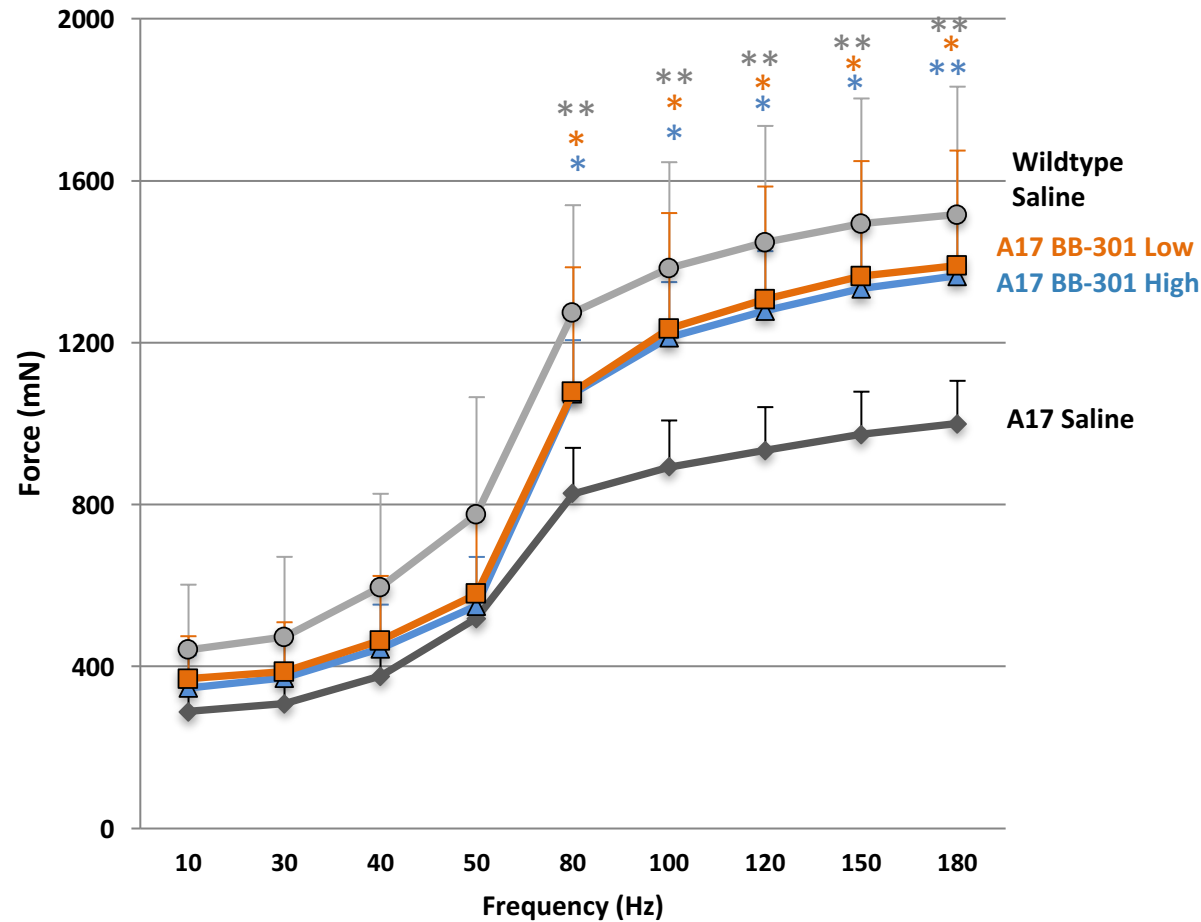


# Intranuclear Inclusions are Resolved in A17 Mice Treated with BB-301

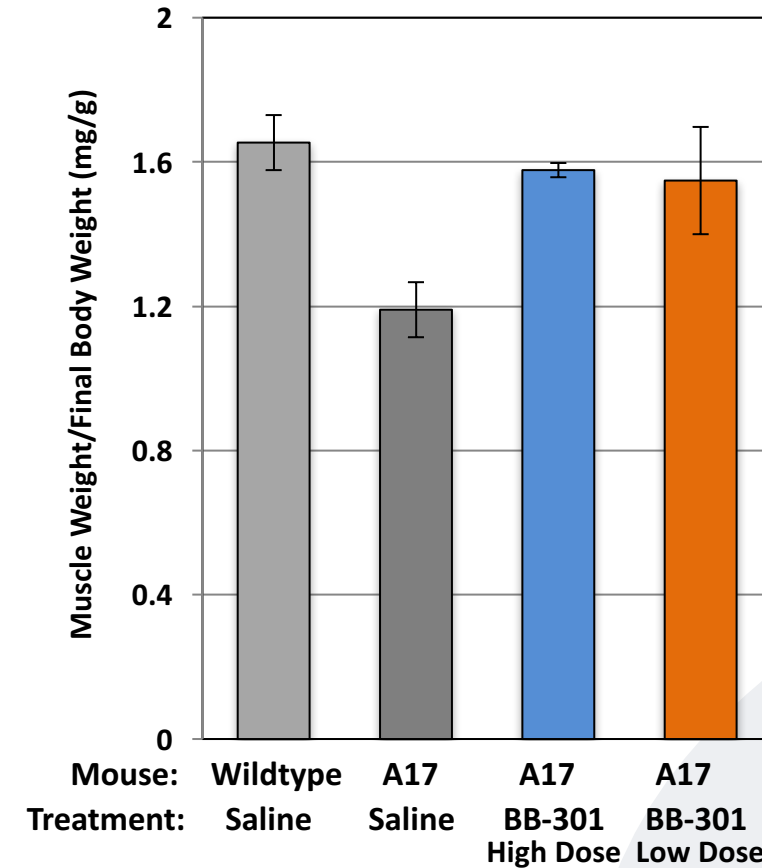


# BB-301 Treatment Restores Muscle Force and Muscle Weight in A17 Mice

## Restoration of Muscle Force



## Restoration of Muscle Weight



# Oculopharyngeal Muscular Dystrophy

## Clinical Candidate BB-301: Product Overview

### Oculopharyngeal Muscular Dystrophy

- Rare, autosomal dominant, monogenic disease
- Estimated 12,000 patients in Western countries
- Eyelid drooping, swallowing difficulties, proximal limb weakness, death due to aspiration pneumonia & 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

# Multiple Shots on Goal

## Longer Term Milestones 2017-2019

	2017	2018	2019
<b>HNSCC</b> <b>BB-401 (EGFR-AS)</b>	<ul style="list-style-type: none"> <li>• IND filing</li> </ul>	<ul style="list-style-type: none"> <li>• Phase 2 initiation</li> </ul>	<ul style="list-style-type: none"> <li>• Phase 2 completion</li> </ul>
<b>HNSCC</b> <b>BB-501 (ddRNAi EGFR)</b>	<ul style="list-style-type: none"> <li>• Discovery</li> <li>• Preclinical POC</li> </ul>	<ul style="list-style-type: none"> <li>• IND-enabling studies</li> </ul>	<ul style="list-style-type: none"> <li>• Phase 1/2 initiation</li> </ul>
<b>OPMD</b> <b>BB-301</b>	<ul style="list-style-type: none"> <li>• Pre-IND meetings</li> </ul>	<ul style="list-style-type: none"> <li>• IND enabling studies</li> <li>• Phase 1/2 initiation</li> </ul>	<ul style="list-style-type: none"> <li>• Phase 1/2</li> </ul>
<b>AMD</b> <b>BB-201</b>	<ul style="list-style-type: none"> <li>• Preclinical POC</li> <li>• Pre-IND meetings</li> </ul>	<ul style="list-style-type: none"> <li>• IND enabling studies</li> <li>• Phase 1/2 Ready</li> </ul>	<ul style="list-style-type: none"> <li>• Phase 1/2</li> </ul>
<b>Hepatitis B</b> <b>BB-103</b>	<ul style="list-style-type: none"> <li>• IND-enabling studies</li> </ul>	<ul style="list-style-type: none"> <li>• Phase 1/2 Ready</li> </ul>	<ul style="list-style-type: none"> <li>• Phase 1/2</li> </ul>



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