

## BENITEC PRESENTATION AT BIOTECH SHOWCASE, SAN FRANCISCO

**Sydney Australia, 16 January 2015:** ddRNAi therapeutics company Benitec Biopharma Limited (ASX: BLT, OTC: BTEBY) is pleased to report that Dr Peter French, Benitec's CEO and Managing Director, yesterday presented a company overview at the Biotech Showcase held in San Francisco in conjunction with the JP Morgan biotechnology conference.

The presentation is attached.

For further information regarding Benitec and its activities, please contact the persons below, or visit the Benitec website at [www.benitec.com](http://www.benitec.com)

<i><b>Company</b></i>	<i><b>Investor relations</b></i>
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### ***About Benitec Biopharma Limited:***

Benitec Biopharma Limited is an ASX-listed biotechnology company (ASX:BLT; OTC:BTEBY) which has developed a patented gene silencing technology called ddRNAi or 'expressed RNAi'. ddRNAi has the potential to produce 'single-shot' treatments and even cures for a range of chronic and life-threatening human conditions. Based in Sydney, Australia with labs in Hayward CA (USA) and collaborators and licensees around the world, the company is developing ddRNAi-based therapeutics for diseases including hepatitis C and B, drug resistant lung cancer, wet age-related macular degeneration and oculopharyngeal muscular dystrophy. Benitec has also licensed ddRNAi to other biopharmaceutical companies for human therapeutic applications including HIV/AIDS, Huntington's Disease, cancer, chronic neuropathic pain and retinitis pigmentosa. For more information visit [www.benitec.com](http://www.benitec.com).



## GENE SILENCING: A quiet revolution in healthcare

## Forward looking statement

This presentation contains forward looking statements that involve risks and uncertainties.

Although we believe that the expectations reflected in the forward looking statements are reasonable at this time, Benitec Biopharma can give no assurance that these expectations will prove to be correct.

Actual results could differ materially from those anticipated. Reasons may include risks associated with drug development and manufacture, risks inherent in the regulatory processes, delays in clinical trials, risks associated with patent protection, future capital needs or other general risks or factors.

This document does not constitute an offer, solicitation or recommendation in relation to the subscription, purchase or sale of securities in any jurisdiction. Neither this presentation nor anything in it will form any part of any contract for the acquisition of securities.

# Company Financial Snapshot



Key financial details	ASX:BLT OTC: BTEBY
Share Price as of 9 <sup>th</sup> January 2015:	AUD \$0.97
Market Capitalisation as at 9 <sup>th</sup> January 2015:	AUD \$112M
Issued Securities as at 21 <sup>st</sup> August 2014:	
Ordinary shares	115,218,993
Options	22,695,098
Cash balance at 30 <sup>th</sup> June 2014:	AUD \$31.3 M

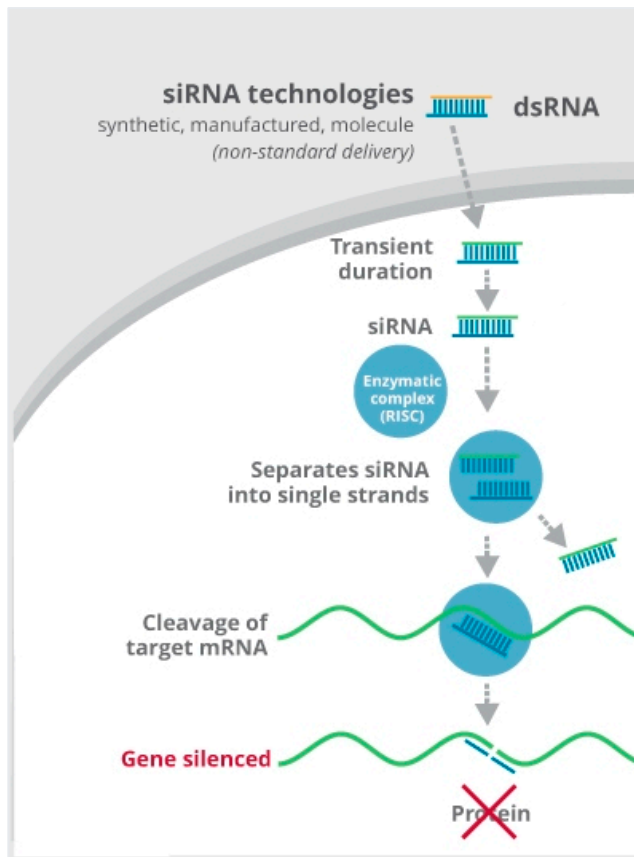


# Strong Investment Case



- Patented gene silencing technology ddRNAi for treatment, 'single shot cure' for human disease
- Hepatitis C (TT-034) Phase I/IIa trial status – 3<sup>rd</sup> patient dosed
- Successful TT-034 trial will validate approach for hepatitis C and broader human diseases
- AUD \$31.5m funding achieved in Feb 2014 will take TT-034 trial to Phase IIb and progress other programs & platform development
- Pipeline of 'company making' programs focused on 'significant' diseases with a high unmet clinical need
- RNAi space 'heats up' due to positive clinical trial data from other RNAi companies

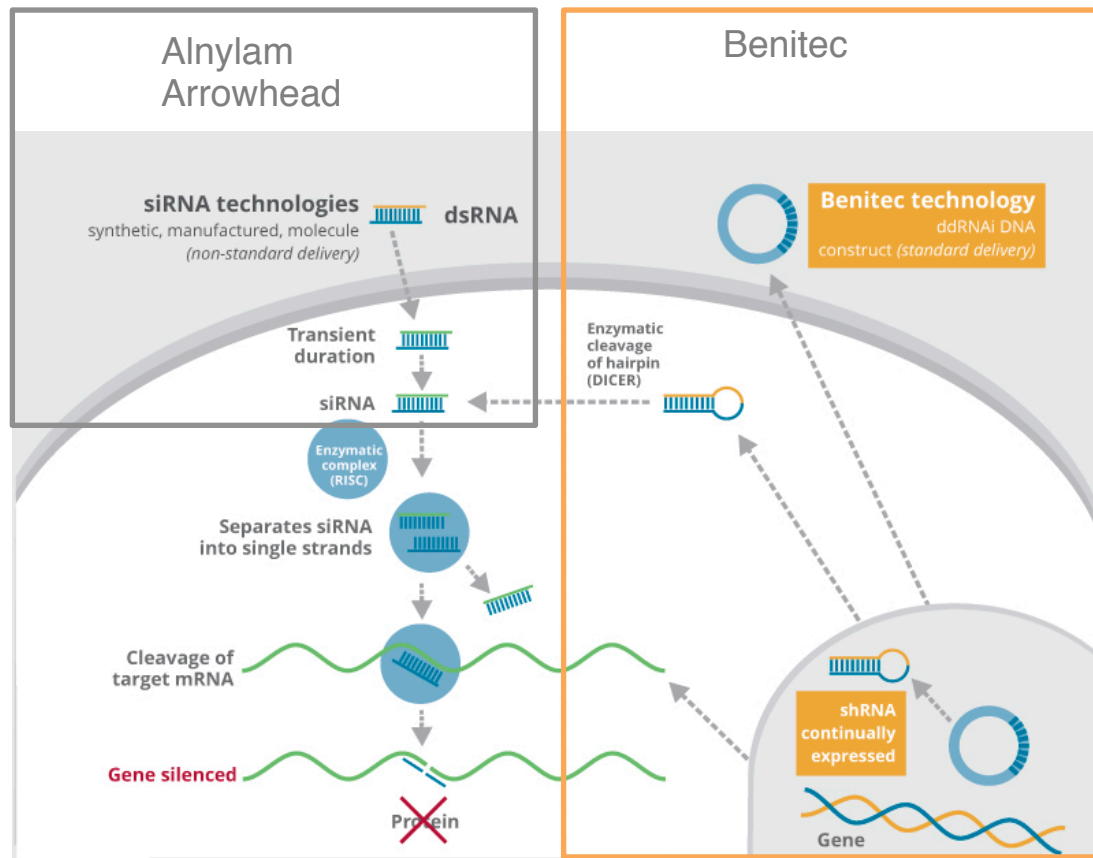
# RNAi: the revolution in medicine Pt 1



## Fire and Mello:

- Published RNAi 1998
- Awarded Nobel Prize 2006

# RNAi: the revolution in medicine Pt 2



Graham & Suhy

- MG develops ddRNAi mid 1990's
- DS develops TT-034 mid 2000s

# ddRNAi: the gene-silencing revolution

## ddRNAi technology:

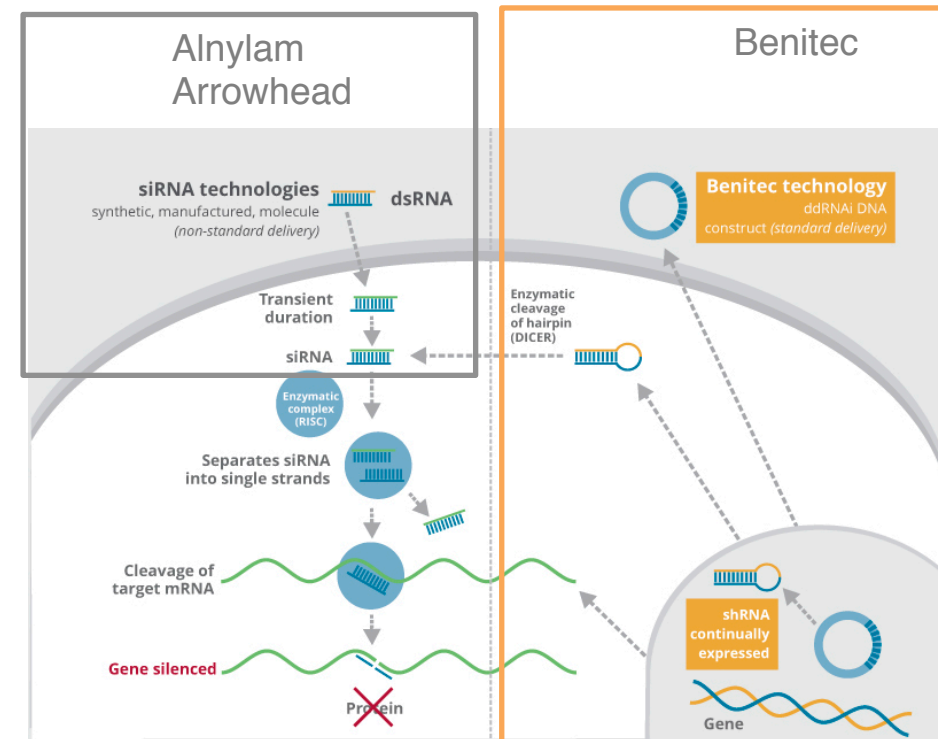
- 'Turns off' disease-associated genes
- Uses power & specificity of RNAi

## ddRNAi avoids RNAi's problems:

- More specific delivery
- Fewer side effects
- Longer lasting (for life of target cells)

## Unique benefits:

- Multiple therapy in one molecule (one gene, multiple sites, multiple genes)
- Protected by over 100 patents (technology & specific diseases)



# Value, investment & opportunity



Company	Technology	Stage	Market Cap (US \$M)
Alnylam	siRNA	Phase II	7,820
Isis	Antisense	Phase II/III	8,500
Arrowhead	siRNA	Phase I	436.46
Dicerna	siRNA	Pre-clinical	328.62
Silence	siRNA	Pre-clinical	157.11
Benitec	ddRNAi	Phase I/IIa	95.2*

# Advanced in-house programs



Focus	Indication	Partners / Collaborators	Discovery	Pre-clinical	Clinical
Infectious Disease	Hepatitis C				
	Hepatitis B	Biomics Biotechnology (JV)			
Cancer	Drug Resistant Lung Cancer	University of New South Wales (RC)			
Ocular Disease	AMD				
Genetic Disease	OPMD	Royal Holloway London University (RC)			

# Sub-licensed Programs



Focus	Indication	Partners/Collaborators	Discovery	Pre-clinical	Clinical
Infectious Disease	HIV/AIDS	Licensed to Calimmune			
Cancer	Cancer Vaccines	Licensed to Regen BioPharma			
Ocular Disease	Retinitis Pigmentosa	Licensed to Genable			
Genetic Disease	Huntington's Disease	Licensed to uniQure			
Neuropathic Pain	Sodium NAV 1.7 Ion Channel	Licensed to Circuit			

# Hepatitis C - TT-034



## **TT-034 is an RNAi therapeutic that is intended as a “one-shot-cure”**

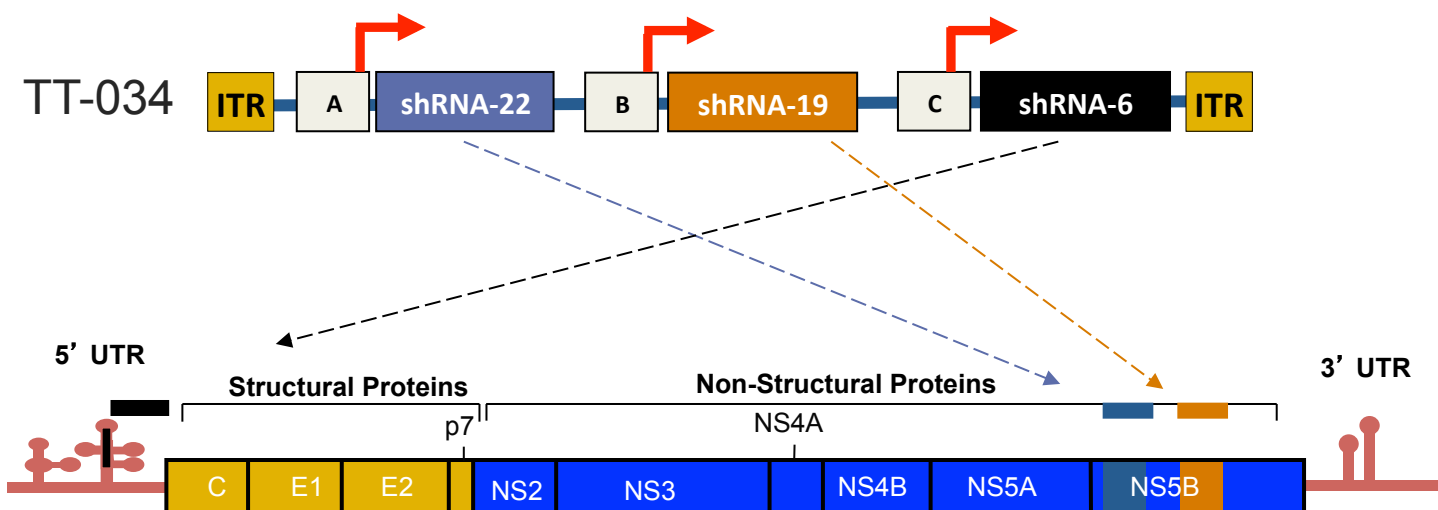
- Recombinant AAV genome delivered via an AAV8 vector (high liver tropism)
- Continuously produces anti-viral shRNAs for over 180 days
- shRNA targets three separate, well conserved regions of HCV RNA
- Near complete liver cell coverage

## **Goal is to achieve complete and sustained elimination of virus with a single infusion**

- Eliminates long treatment courses and patient compliance issues
- Very low toxicity in animal studies
- Potential for combination with small molecule therapies for enhanced efficacy

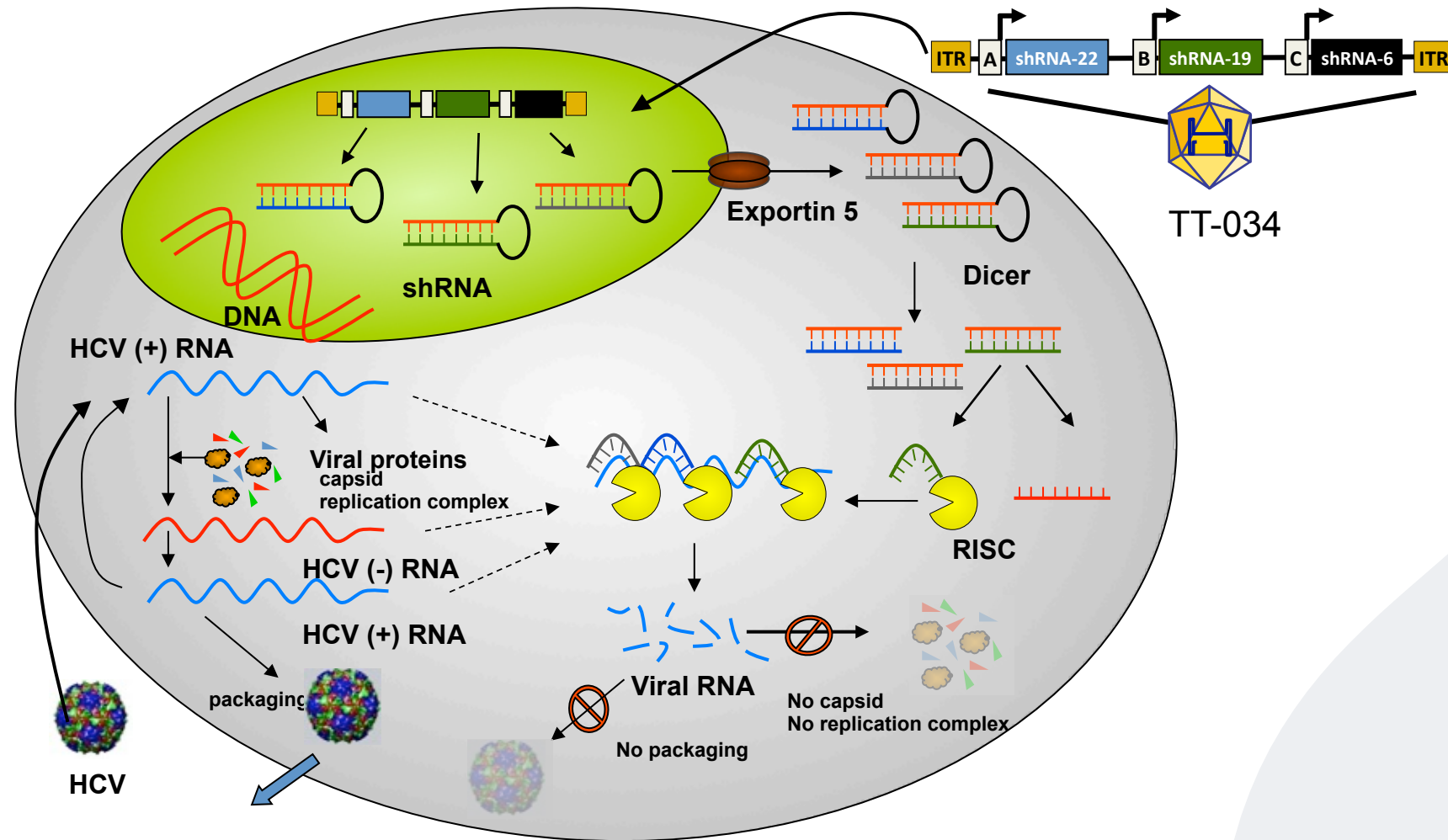


# Design of TT-034



- Three independently transcribed RNAi elements target three separate, well-conserved regions of the HCV genome; **helps prevent the generation of viral escape mutants**
- Combination drug in one therapeutic entity provides broad patient applicability, while maintaining specificity
- Patent to 2026

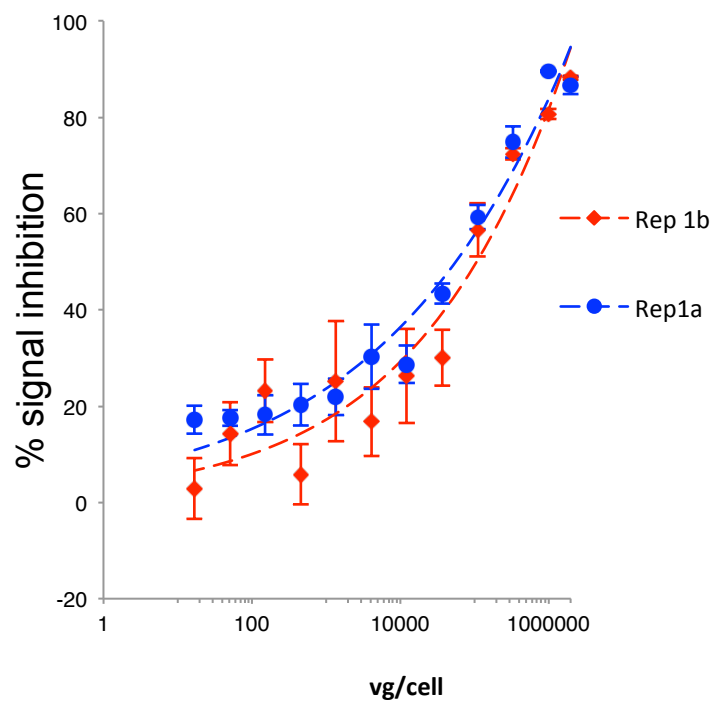
# MOA of TT-034 Against HCV



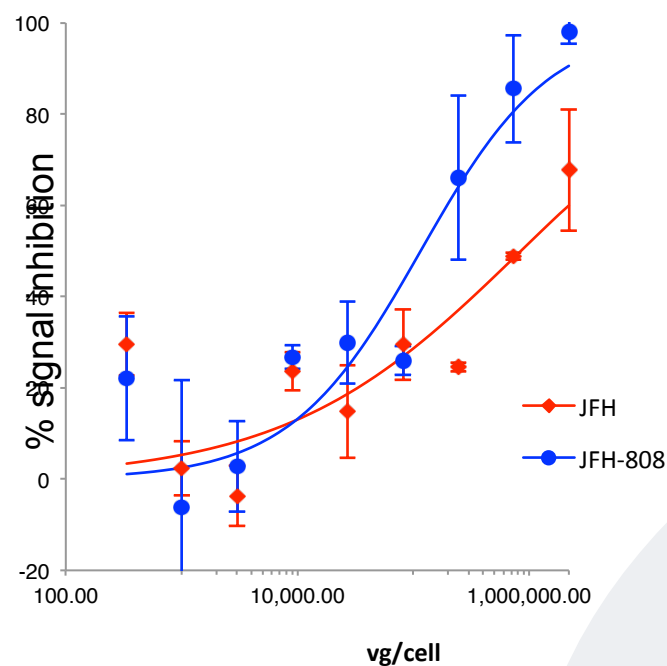
# TT-034 Activity Against HCV Genotype 1a and 1b



**HCV replicon**  
(representative data)



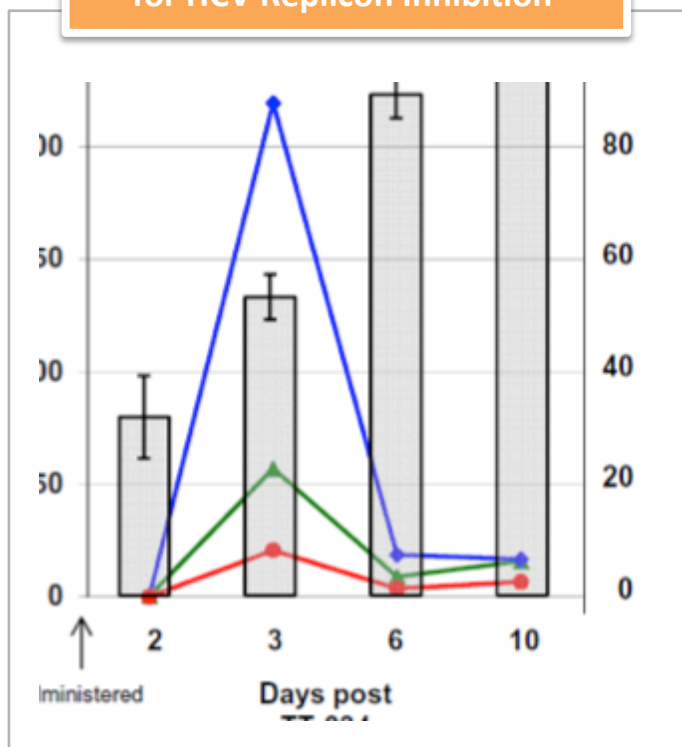
**HCVcc**  
(representative data)



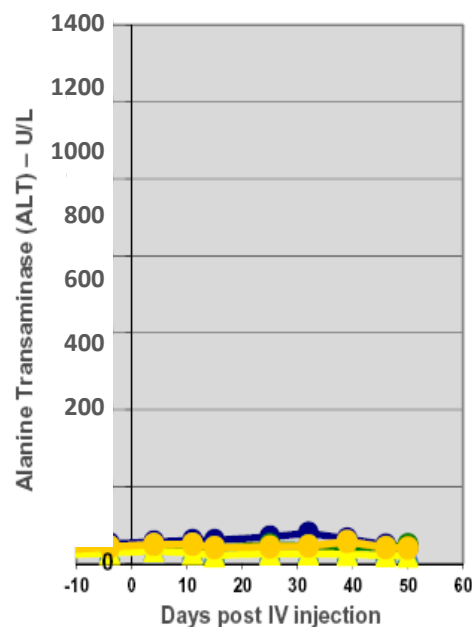
# TT-034: Pre-clinical efficacy and safety

- Clinically relevant doses of TT-034 produce sustained levels of HCV inhibition without toxicity

Quantities of shRNA/cell required for HCV Replicon Inhibition



Assessment of liver toxicity in cynomolgus monkeys



shRNA/cell in cynomolgus monkey livers at day 50

	shRNA-6	shRNA-22	shRNA-19
1.25x10 <sup>11</sup> vg/kg	18	66	9
1.25x10 <sup>11</sup> vg/kg	782	1223	196
6.25x10 <sup>12</sup> vg/kg	8350	6090	1463

Avg. from dose cohort

# Phase I/IIa Dose Cohorts



Cohort	Dose (vg/kg)	Dose escalation step (log 10)	Total No subjects	Dosing scheme for subjects	Observation period per subject and between cohorts before dose escalation
1	$4.00 \times 10^{10}$	Starting dose	2	Sequential (1+1)	6 weeks
2	$1.25 \times 10^{11}$	0.5	3	Sequential and parallel (1+2)	6 weeks
3	$4.00 \times 10^{11}$	0.5	3	Sequential and parallel (1+2)	6 weeks
4	$1.25 \times 10^{12}$	0.5	3	Sequential and parallel (1+2)	10 weeks
5	$4.00 \times 10^{12}$	0.5	3	Sequential and parallel (1+2)	10 weeks

- DSMB review after first patient in each cohort and between cohorts
- Extensive safety monitoring during 24 weeks observation

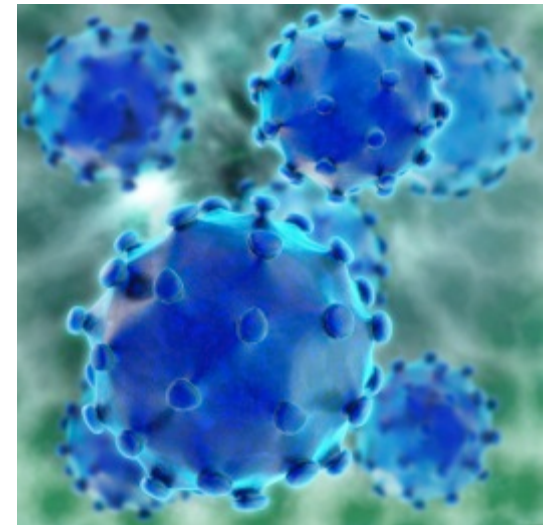
# TT-034 Trial Endpoints

## Primary Endpoints (Safety):

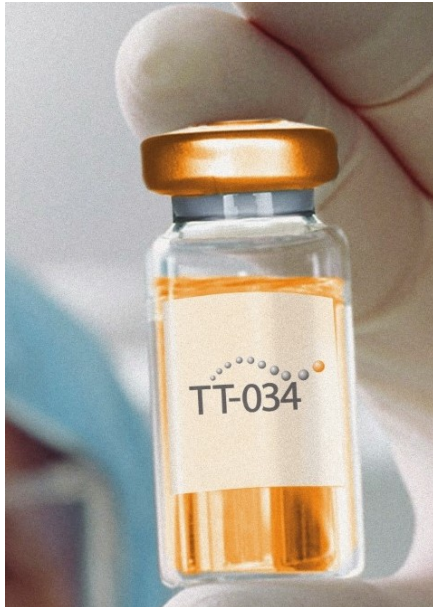
- Incidence of adverse events
- Changes in clinical parameters

## Secondary Endpoints (Efficacy):

- Sustained reduction in HCV viral load in the blood
- Assessment of TT-034 levels in liver biopsy
- Assessment of shRNA expression in liver biopsy
- shRNA expression levels in serum (exosomes)



# Hepatitis C – TT-034 Update



## Open-label dose-escalation Phase I/IIa trial underway:

- Protocol reviewed, approved by NIH RAC, unanimous panel support
- FDA released IND January 12, 2014
- Patient dosing commenced May 29, 201
- DSMB recommended study continue, no modification July 21, 2014
- 3<sup>rd</sup> patient dosed January, 2015

## US-based trial sites

- Duke Clinical Research Unit, North Carolina - 2<sup>nd</sup> patient dosed
- University of California, San Diego – screening patients
- More sites being brought on to expedite patient recruitment

# TT-034: 2013 Clinical Trial Implications



**TT-034 is a “Disruptive Technology”  
in a market that will remain very  
large**

**As a “single shot cure,” TT-034 will  
supersede small molecule  
cocktails**

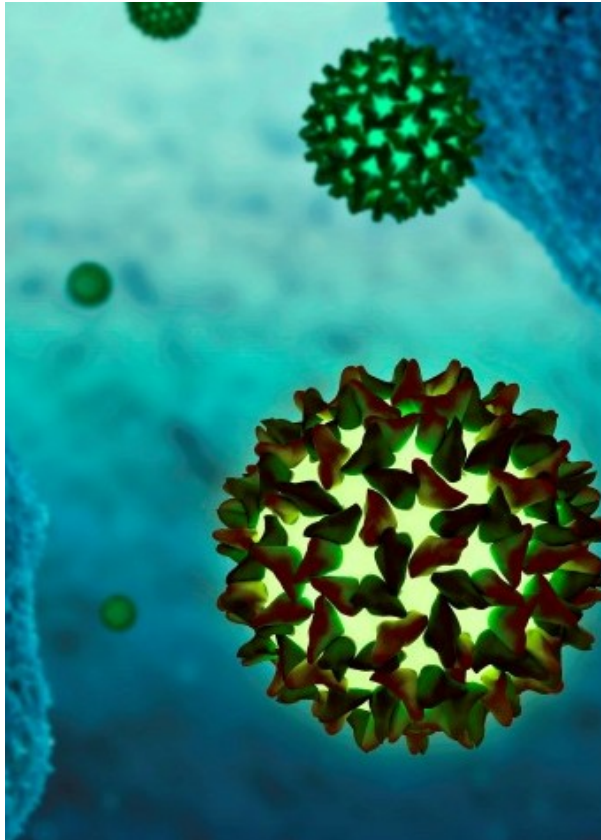
Superior side effect profile and efficacy

Competitively priced and offers significant clinical and  
compliance advantages





# Hepatitis B (HBV)



## Context

- 350 million infected worldwide, major unmet medical need
- Substantial interest from big pharma

## Approach

- Replicate, leverage Hep C approach
- Leverage RNAi success, add extra benefits of ddRNAi

## Status

- Homology search for sequence validation complete
- Optimisation of DNA constructs underway
- Animal model for HBV identified.

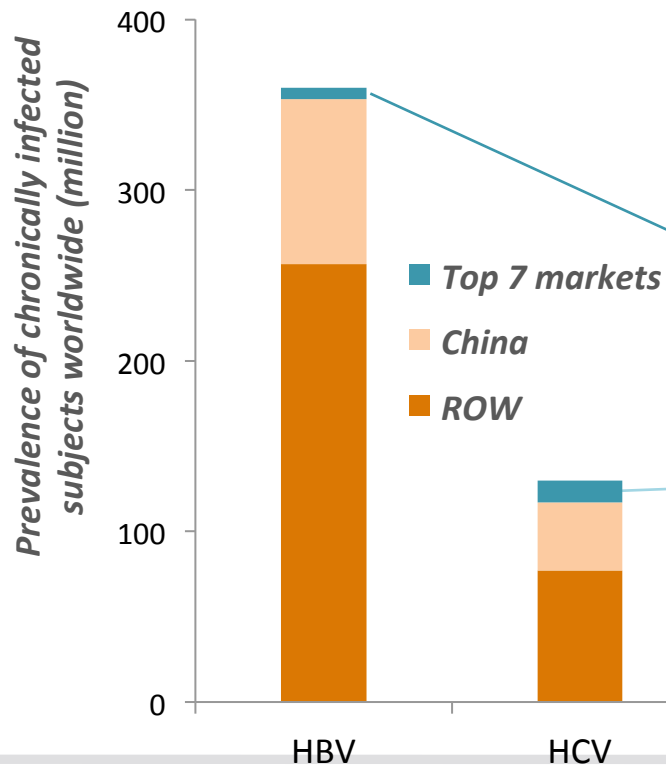
# Hepatitis C and B

## Significant Commercial Opportunities



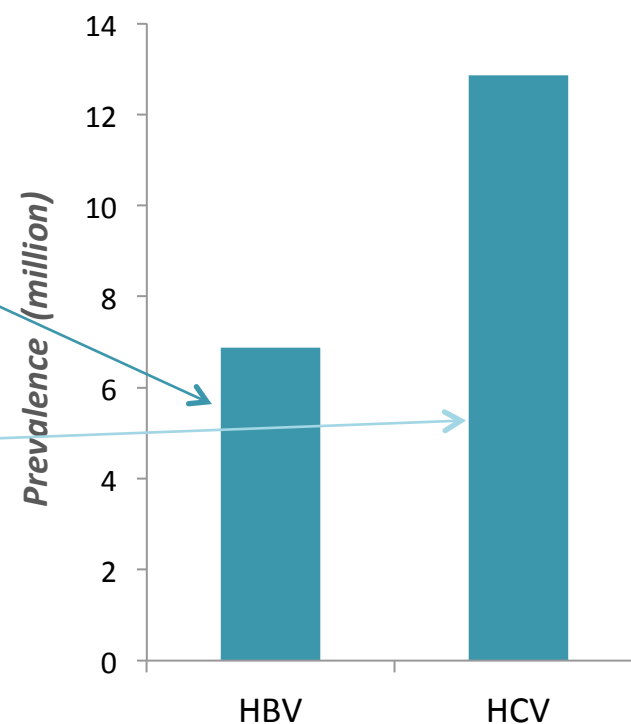
Worldwide, HBV is three times more prevalent than HCV

*Chronic HBV and HCV prevalence worldwide*



In the top Western markets HCV is two times more prevalent than HBV

*HBV and HCV prevalence in top 7 markets\**



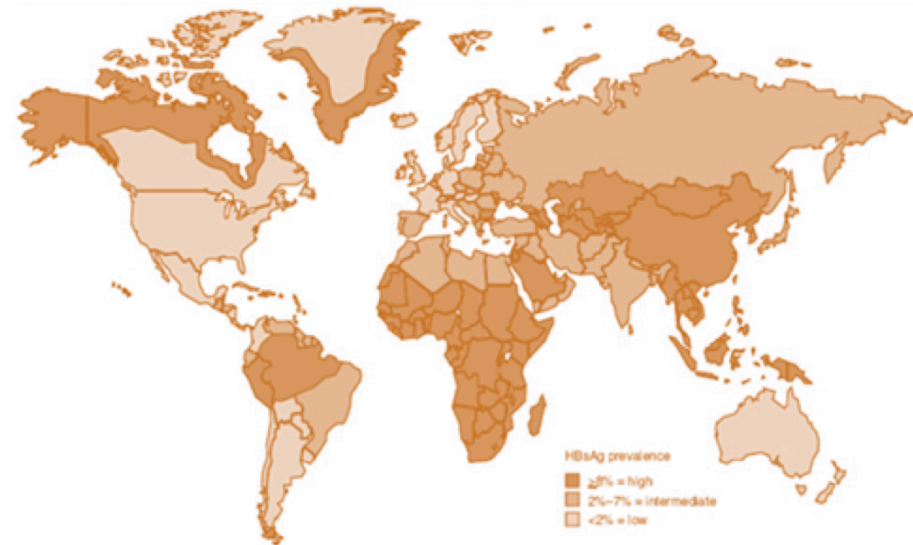
# Chronic hepatitis B market overview

Despite the existence of a vaccine against the HBV, the prevalence rate in the population remains high. HBV infection ranks second only to tobacco as a known human carcinogen.

## Chronic HBV Infection Incidence and Prevalence

- **350 million people worldwide are chronically infected** and become carriers of the virus.
- In the USA there are > 60,000 new cases p.a.
- HBV causes 60-80% of the world's primary liver cancers.
- 1 million people p.a. worldwide **die from chronic active hepatitis, cirrhosis or HBV-induced liver cancer.**

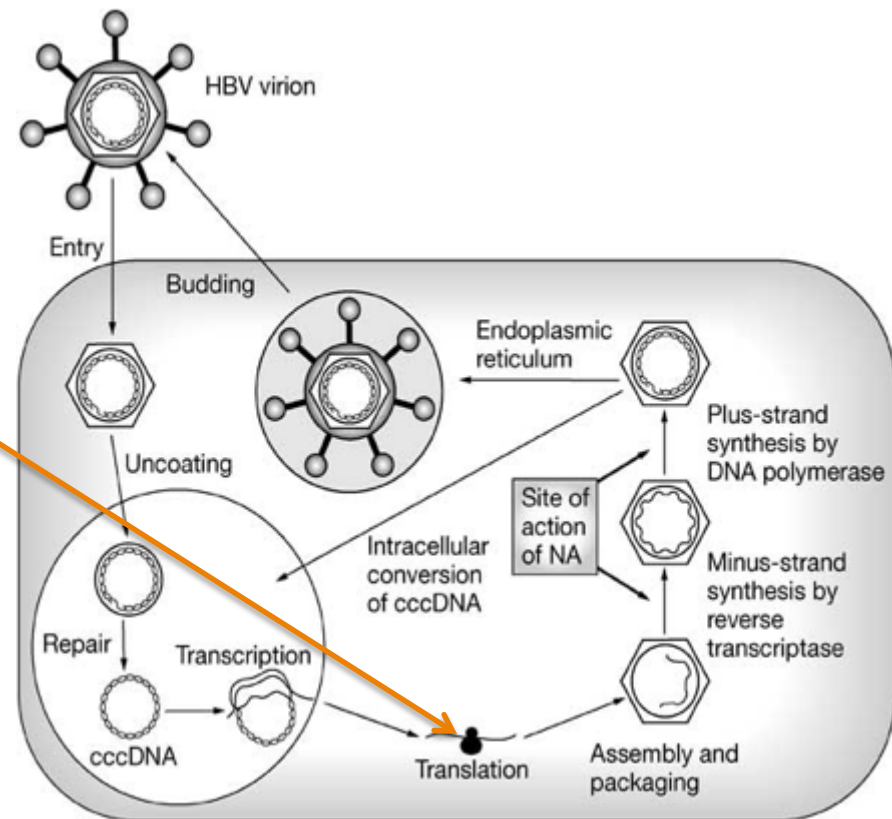
## Geographic distribution of chronic HBV infection



Approximately 1 in 3 people get infected with HBV during their lifetime

# The rationale for RNAi in HBV Therapy

- Increased pharma investment and interest in novel treatments for chronic hepatitis B.
  - RNAi is one of the most promising.
- HBV is susceptible to RNAi because it replicates via an **RNA intermediate**.
- siRNA needs repeated doses indefinitely.
- ddRNAi can provide a single dose treatment to silence HBV mRNA long term.



# The target gene for a ddRNAi-based HBV therapeutic

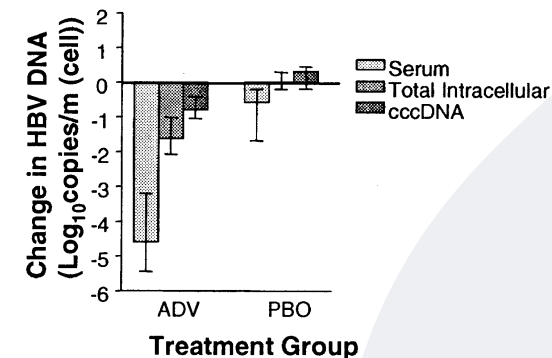
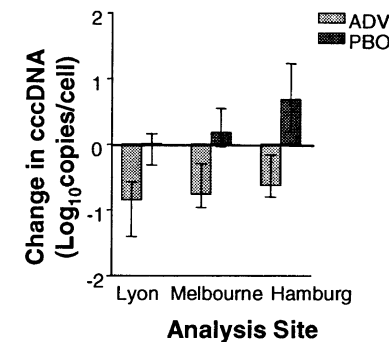


## Long term suppression of viral replication can induce decrease in cccDNA

48 weeks of continuous therapy with the nucleotide analogue adefovir dipivoxil (ADV) resulted in an **84% decrease in cccDNA** in HBV infected patients, and a **94% decrease in circulating HBsAg\***.

ADV is a potent HBV polymerase inhibitor.

This provides evidence that sustained repression of viral replication through inhibition of the HBV DNA polymerase could significantly reduce the amount of cccDNA present in infected hepatocytes.



# The target gene for a ddRNAi-based HBV therapeutic

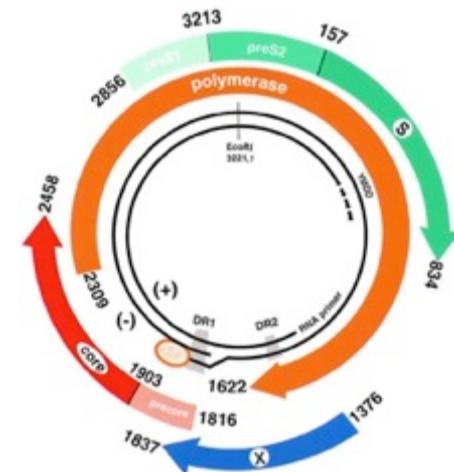


Benitec has identified the HBV RNA-dependent DNA polymerase as a key target to address the unmet need in chronic HBV infection treatment.

## HBV DNA polymerase gene

- The hepatitis B virus genome encodes four open reading frames; *core*, *polymerase*, *surface* and *X* protein
- The pregenomic mRNA serves for translation of the core protein, the surface antigen and the polymerase-reverse transcriptase, and also represents the template of reverse transcription. Therefore, it makes an ***excellent target for a gene silencing*** approach.
- The mechanism of RNA-directed DNA synthesis has been well characterised and plays a unique and essential role in the viral replication cycle.
- ***Additional gene targets can be incorporated into the DNA construct to allow for more efficient inhibition of viral replication.***

## Hepatitis B Virus Genome Map



# ddRNAi Chronic HBV Infection Product Preclinical Studies — Results to date

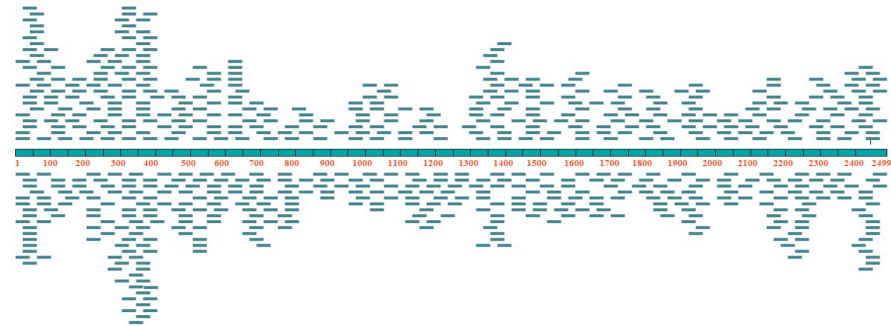


These preclinical studies demonstrate the potential of HBV DNA polymerase-targeted ddRNAi to achieve inhibition of viral replication.

## Step 1: Large Scale Sequencing

5000 clones were sequenced and **642 non-repeat siRNA targets** were obtained, randomly distributed along the target gene.

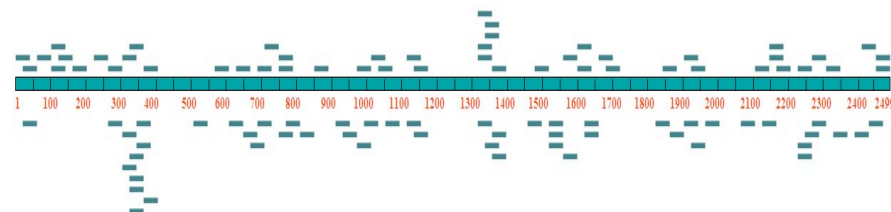
### Hepatitis B virus siRNAs Polymerase Domain (2499bp):



642 siRNA clones

## Step 2: Target Screening by siRNA Expression Cassettes (SECs)

100 siRNA sequences were identified that produced >50% HBV mRNA knock down, 14 of which resulted in **>70% knock down**.





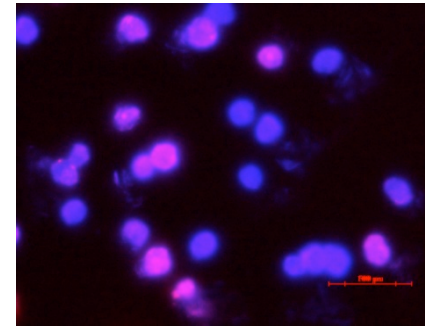
# ddRNAi Chronic HBV Infection Product Preclinical Studies — Results to date



These preclinical studies demonstrate the potential of HBV DNA polymerase-targeted ddRNAi to achieve inhibition of viral replication.

## Step 3: Large Scale Screening using SECs

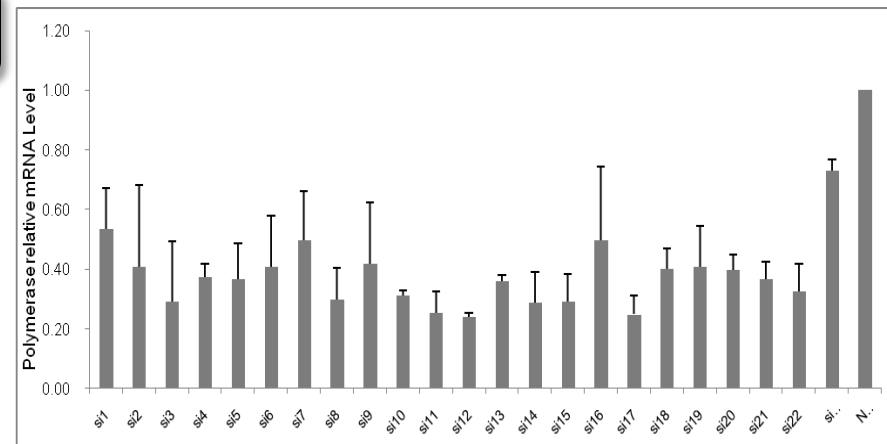
The **14 most effective siRNA sequences were identified** through transfection of HepG2 2.2.15 cells with siRNA expression cassettes.



Transfection efficiency in optimal conditions is >70%

## Step 4: Activity Validation With Chemically Synthesized siRNA

The activity of selected sequences was validated through quadruplicate independent transductions with chemically synthesized siRNA. **Fourteen candidate siRNAs were selected** as the basis for gene construct design. A patent application has been filed.





# Drug Resistant Lung Cancer



- Lung cancer is the most common cancer worldwide
- With around 65% of patients dying within one year of diagnosis, non-small cell lung cancer is the leading cause of cancer-related deaths worldwide (1.3 million deaths p.a.)
- The rapid emergence of drug resistance cancer cells provides a major challenge in the treatment of non small cell lung cancer.
- The efficiency of existing chemotherapeutic agents is restricted by dose limiting systemic toxicity. A significant opportunity therefore exists for treatments that enhance the effect of therapeutic drugs and are capable of reducing side effects.

**A significant need exists for a therapy capable of restoring and/or improving the effect of therapeutic drugs in resistant cell lines and minimizing side effects associated with chemotherapy treatment.**

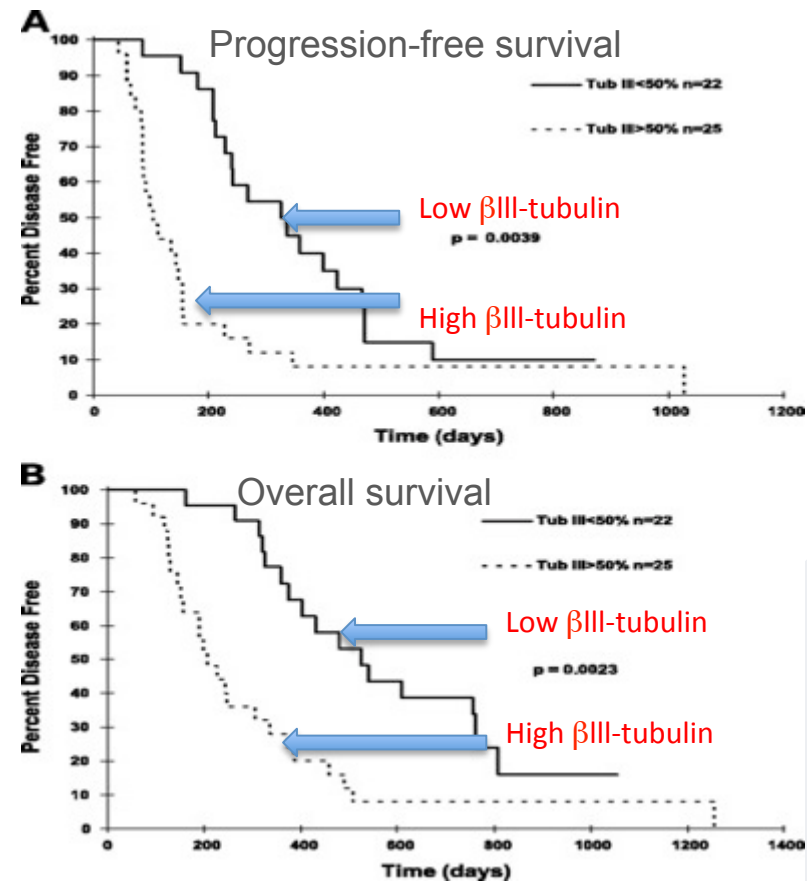
# Target: $\beta$ III-tubulin gene

Resistance to chemotherapy drugs is strongly associated with over-expression of  $\beta$ III-tubulin which appears to act as a tumour pro-survival factor.

Patients with high levels of  $\beta$ III-tubulin show significantly decreased survival.

Inhibition of  $\beta$ III-tubulin by RNAi can restore chemosensitivity.

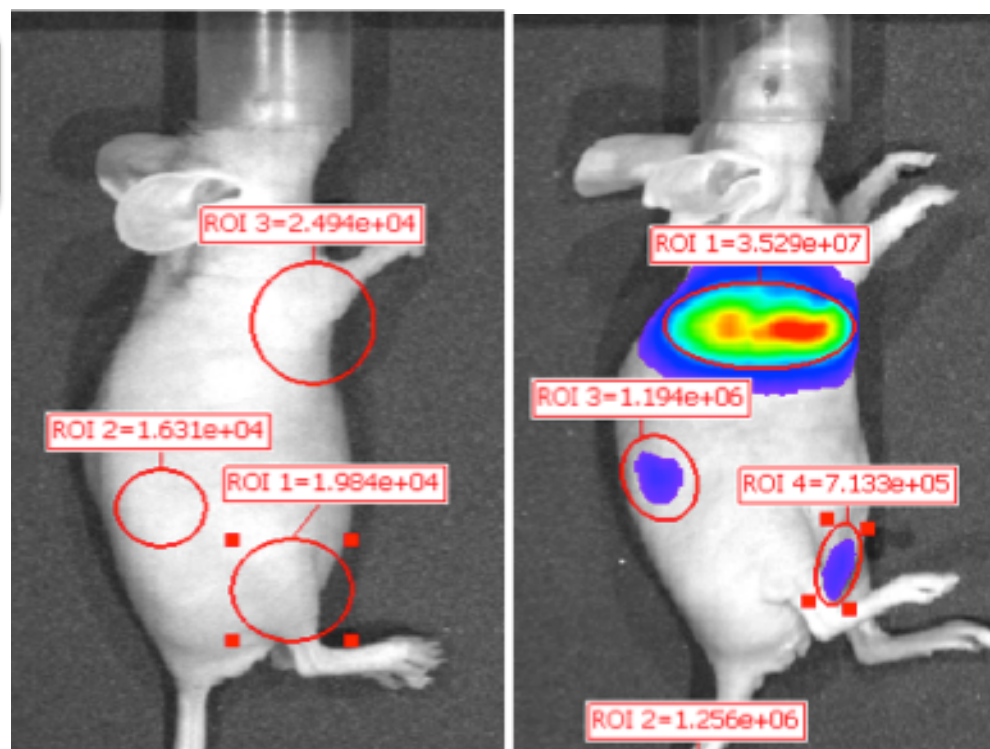
IP licensed from UNSW



Jet-PEI-based complexes can deliver DNA constructs to tumours with very high efficiency

Jet-PEI nanoparticles efficiently deliver plasmid constructs to tumours *in vivo*. Mice were injected i.v. with Jet-PEI complexed with a luciferase-expressing plasmid (pGL4.50; Promega).

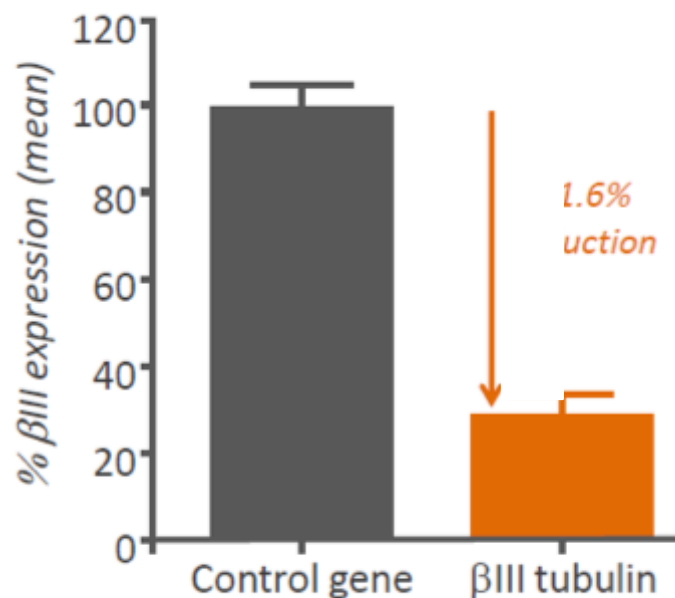
Animals were imaged (Xenogen) 24 hrs after injection. Strong *luc* activity is apparent in tumour-bearing animals (right) but not control animals (left).



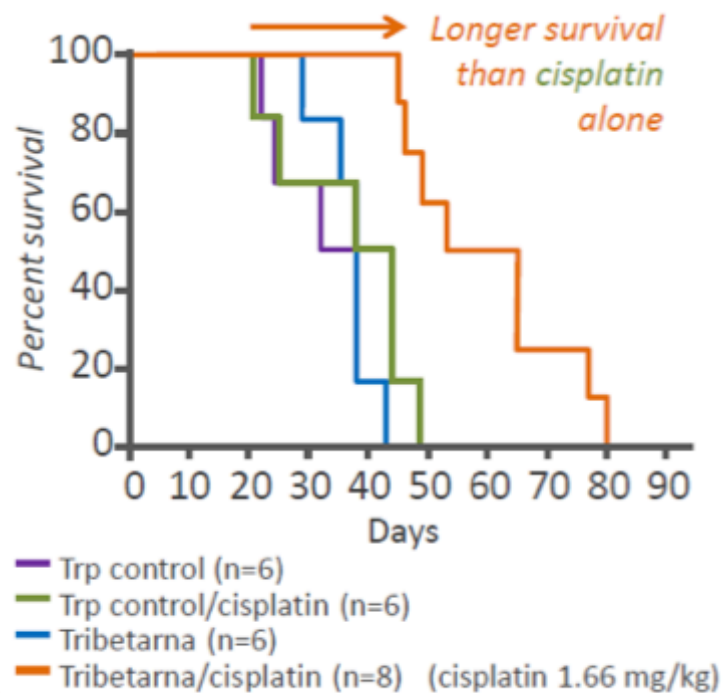
Quantification of *luc* activity indicates 1,000-fold higher enzyme activity in tumours compared to non-involved tissues (data not shown).

## Proof-of-principle is established:

*A single injection of Tribetarna effectively silences the  $\beta$ III tubulin gene in vivo and in vitro*



*Tribetarna™ significantly enhances survival in a preclinical model of lung cancer in combination with chemotherapy*



# Tribetarna™ - Next Steps

**A Phase I/IIa clinical trial of Tribetarna™ in conjunction with cisplatin is planned**

Benitec is committed to conducting a Phase I/IIa clinical trial of Tribetarna™ in combination with cisplatin in patients with advanced NSCLC in Europe.

Patients will receive up to 4 cycles of Tribetarna™ + cisplatin and tumor growth and survival will be assessed.

To achieve this, preclinical safety and toxicity studies are underway.



**With clinical success in lung cancer, this approach can be developed to target other cancers that express high  $\beta$ III tubulin (pancreas, renal, breast, ovarian & gastric)**

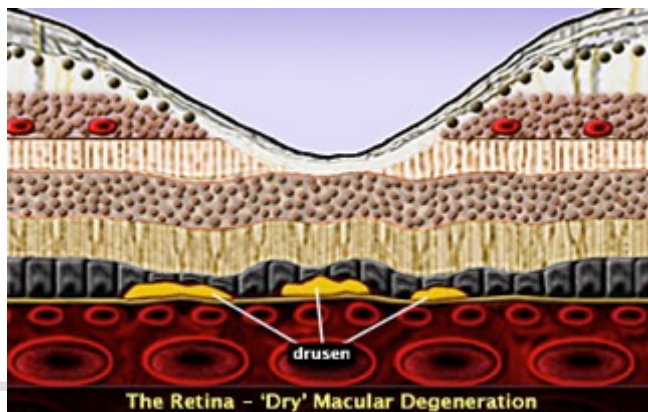
# Age related Macular Degeneration (AMD)

AMD is the leading cause of irreversible vision loss in the US – estimated 1.75M people

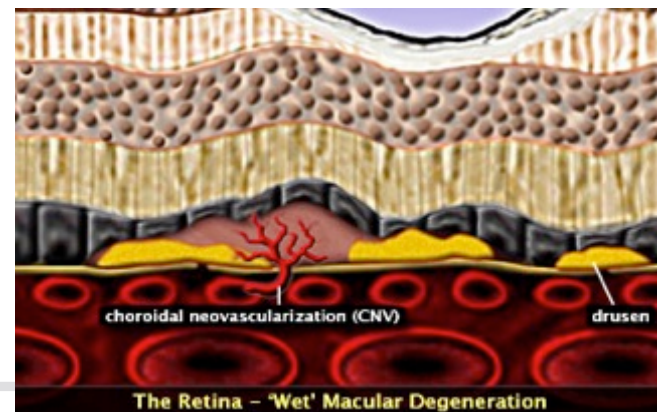
Age related – 10% of people between 60 and 75 and 25% of people >75 years old



**In Dry AMD, drusen deposits start to degrade vision**



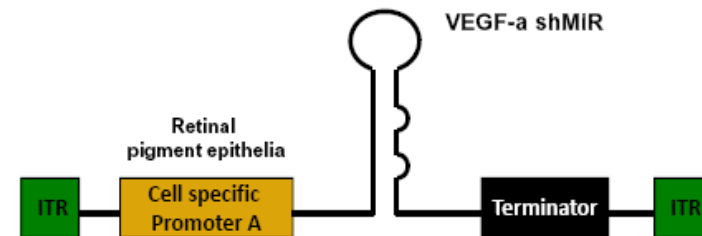
**In Wet AMD, an inflammatory response sets off a cascade on events that further degrades vision through neovascularization**



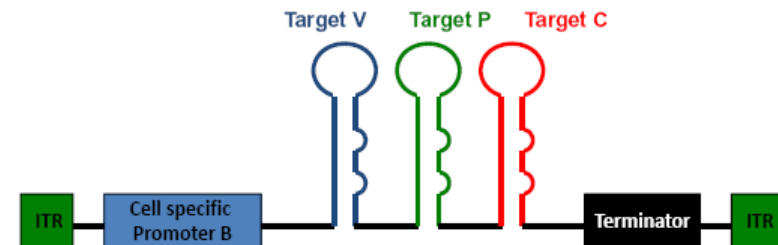


# AMD therapeutics

TT-211 – An AAV-encapsidated construct that expresses a single shRNA modeled into a miRNA backbone that inhibits the expression of VEGF-A



TT-231 – A follow-on product in which an AAV-encapsidated construct expresses three shRNA modeled into three miRNA backbones and inhibit the expression of Target V, Target P, and Target C for the treatment of wet and dry AMD



# AMD Next Steps



- In collaboration with 4D Molecular Therapeutics - developing next generation AAV vectors able to broadly transduce wide range of human retinal cells
- Novel AAV Vectors – increased tissue specificity & reduced immunogenicity
- TT-211 animal model testing to be undertaken directly in NHP model of AMD – service provider identified.



# Oculopharyngeal Muscular Dystrophy (OPMD) Program

A genetic orphan disease (PABPN1 gene defect)

Appears in middle age

Symptoms include severe swallowing difficulties leading to choking

## Prevalence:

Caucasians 1:100,000 in Caucasians (> 4,000 cases in EU and > 2,500 cases in US)

Known clusters: French Canadians (1:1,000 = 5,000 cases), Bukhara Jews (1:600), Hispanics in New Mexico

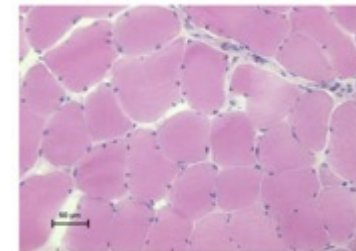
No effective treatment exists - symptomatic surgical interventions (myotomy) are used to correct the ptosis and improve swallowing

Treatment does not correct the progressive degradation of the pharyngeal musculature

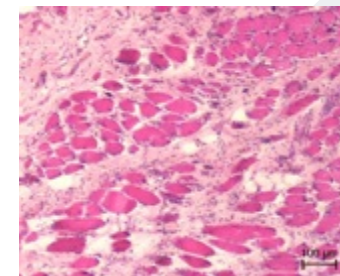
**Very high medical need for effective therapeutics**



Unaffected tissue

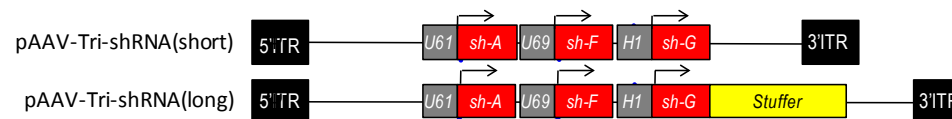


Affected tissue



# ddRNAi constructs silence PABPN1

- A range of constructs have been prepared in AAV and lentiviral gene therapy vectors
- For example, AAV vectors expressing a triple cassette targeting PABPN1

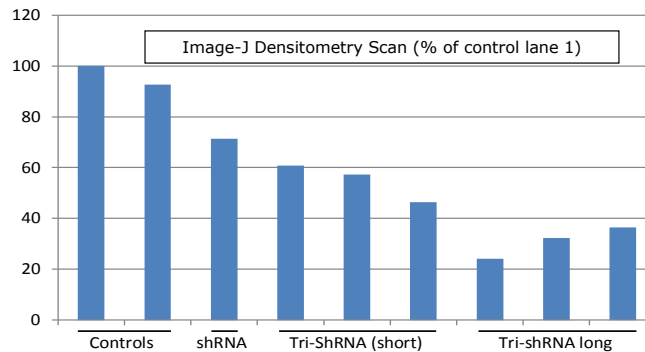


- DNA constructs silence PABPN1 in 293T cells (transient delivery)

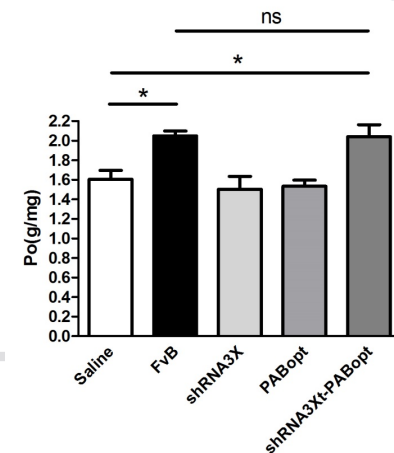
Western blot



Densitometer



- Initial *in vivo* studies of suppression and replacement show efficacy in restoring muscle function



## Commercially-focused Management and Board

### BOARD

#### Chairman:

**Peter Francis**, LLB, Grad Dip.  
(Intellectual Property)  
Partner at Francis Abourizk Lightowlers

#### Directors:

**John Chiplin**, PhD  
Polynoma, Arana, ITI Life Science Fund

**Iain Ross**, BSc, CH.D.  
Silence Therapeutics, Tissue Therapies,  
Ark Therapeutics, Anatara

**Kevin Buchi**  
Cephalon, Teva, Mesoblast, Tetralogic

### MANAGEMENT

**MD and CEO: Peter French, MBA, PhD**  
CSIRO, St Vincent's, Cryosite founder

**CSO: Michael Graham, PhD**  
Inventor of ddRNAi technology  
CSIRO, Benitec founder

**CBO: Carl Stubbings, BSc**  
Panbio, Quest Diagnostics, Focus Diagnostics

**SVP R&D: David Suhy, PhD**  
Tacere Therapeutics, Avocel, Antara  
Biosciences, PPD Discovery

**CFO: Greg West, CA**  
Price Waterhouse, Bankers Trust, Deutsche  
Bank, NZI

# Summary



- Developing RNAi (Nobel Prize-winning technology)
- ddRNAi can provide a 'single shot cure' for many human diseases
- Over 100 patents, patent applications for ddRNAi
- Extensive pipeline of 'company making' programs
- Clinical stage programs (HCV & HIV/AIDS) poised to validate ddRNAi for other diseases
- Well funded (over \$30M from 10 US institutional investors in Feb 2014)
- Internationally credible, experienced Board and Management

# Contact Information



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