BENITEC BIOPHARMA
silencing genes for life™

Rise and Fall and Rise of RNAi: The Benitec Experience

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April 2014

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.

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RNA-based therapies – recent commentary

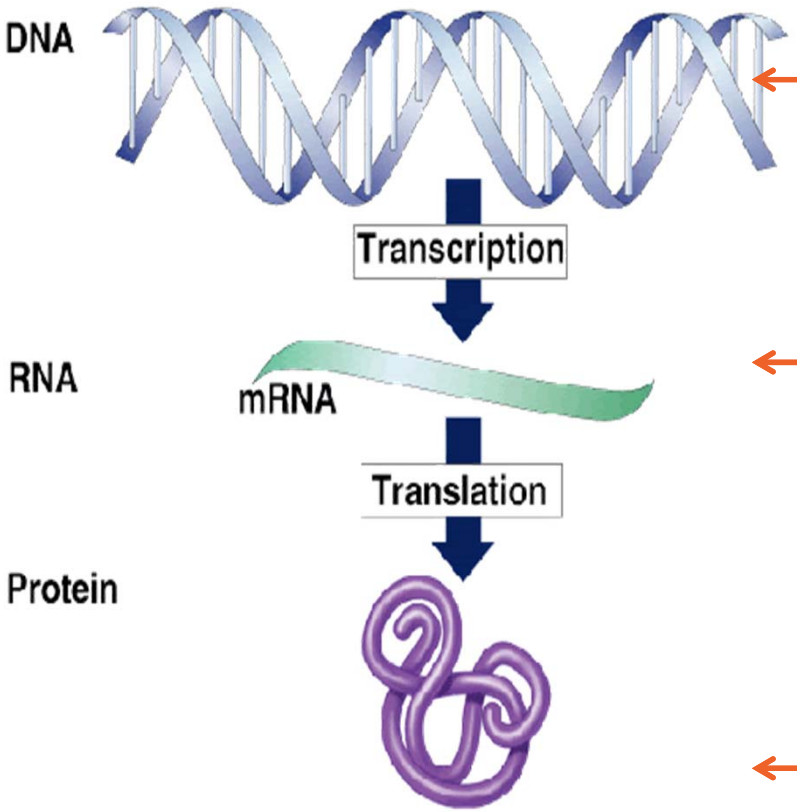
"R&D on RNA therapies took a giant leap with the discovery of RNA interference technology... **The RNA therapeutics market is poised to overtake other conventional therapies and is expected to become one of the fastest growing therapeutic classes in the pharmaceutical market by 2020**." - GBI Research, Feb 1, 2010.

"…**Companies focused on manipulating RNA messages—by RNA interference (RNAi), antisense, or other techniques—have been white hot in an already sizzling biotech sector**." - "BioPharm Executive: Will 2014 Be The Year For RNA Companies?" - Karl Thiel for BioSpace.com

RNA therapies can be divided into:

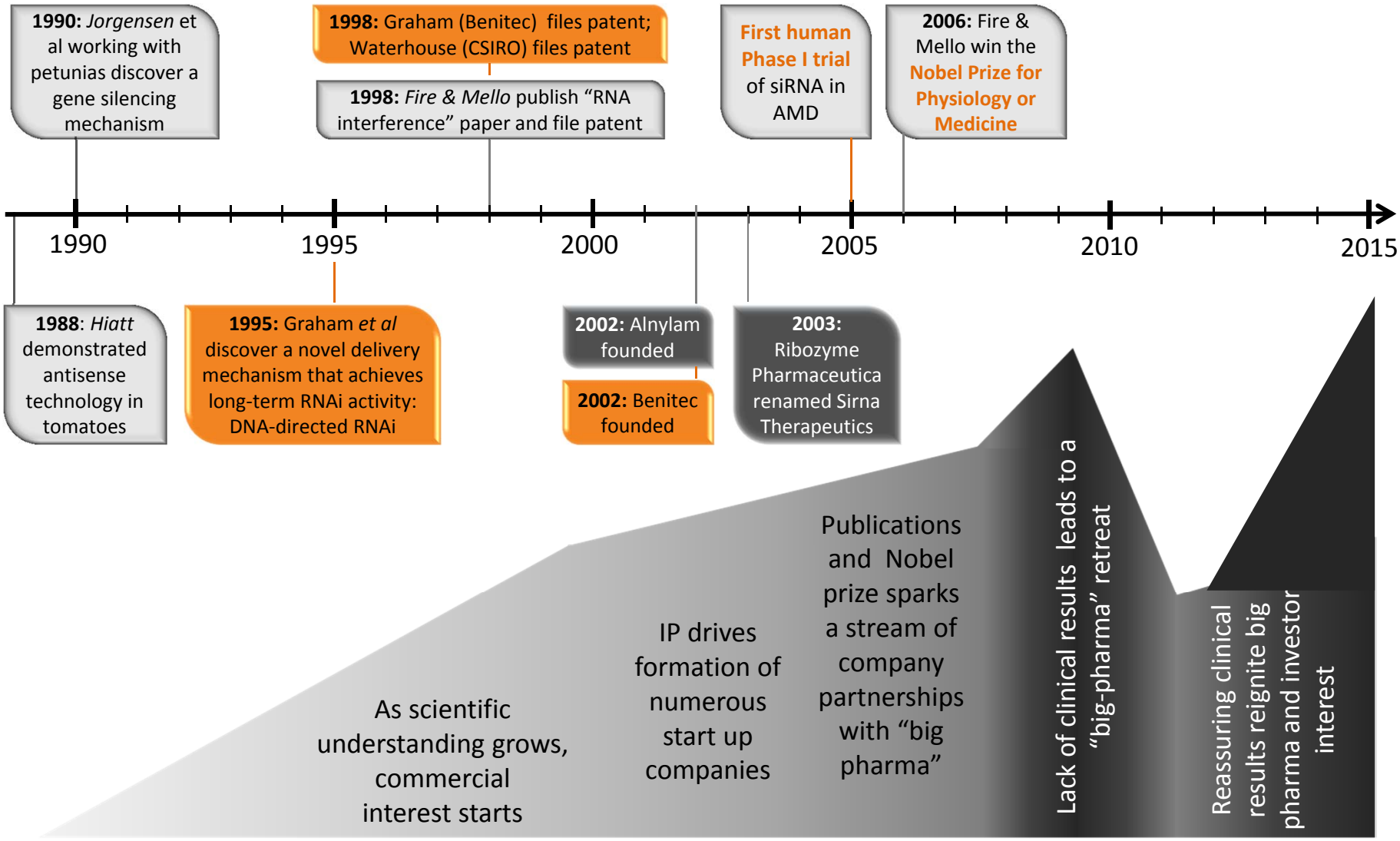
- RNAi therapies, which are mediated by the RISC enzyme
- Antisense therapies, which are RISC-independent agents.

Gene-silencing therapeutic strategies



Technology		Company
Zinc finger nucleases	→	Sangamo
CRISPR	→	Editas Medicine
TALENS	→	-
CRISPR	→	-
DNAZymes, Ribozymes	→	-
Antisense oligonucleotides	→	**Isis**, Santaris, Antisense
mRNA	→	Moderna
siRNA	→	**Alnylam**, Quark, Silence, Rxi, Tekmira, Dicerns
ddRNAi	→	**Benitec**, Calimmune, Genable, Regenerus
Small molecules	→	(various)
Monoclonal antibodies	→	(various)

RNAi timeline



Antisense oligonucleotides

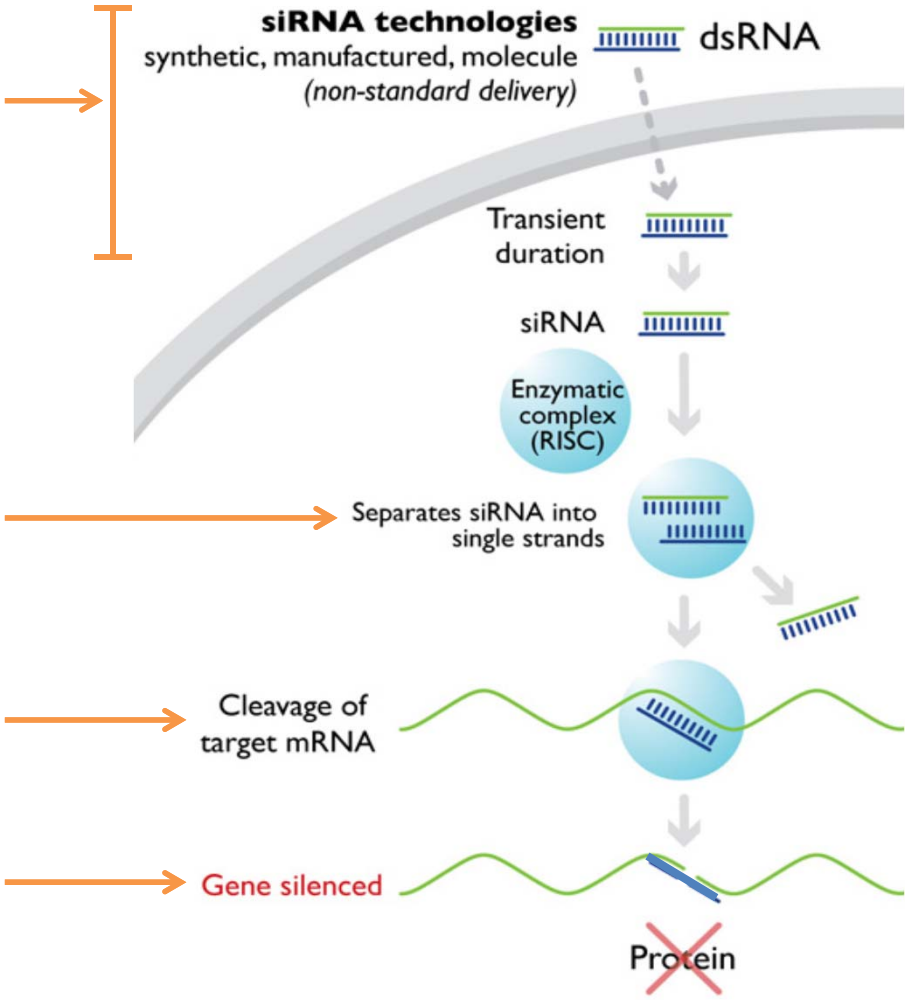
Market Cap: $5,100 M NASDAQ: ISIS

Development Programs:

- **Cardiovascular**
  Hypertriglyceridemia; Coronary Artery Disease; Clotting Disorders; Coronary Artery Disease; Clotting Disorders; Hyperlipidemia
- **Severe and Rare**
  Homozygous FH; Pouchitis; Spinal Muscular Atrophy; Acromegaly; TTR Amyloidosis; Cushing's Syndrome; Hereditary Angioedema; Myotonic Dystrophy Type 1
- **Metabolic**
  Diabetes; Obesity
- **Cancer**
- **Inflammation/other**
  Multiple sclerosis; ocular; HCV

siRNA

- RNAi is triggered by 21–23nt RNA duplexes called small interfering RNA (siRNA)
- siRNA duplexes associate with a multi-protein complex known as the RNA-inducing silencing complex (RISC):
- One strand of the siRNA duplex is loaded into RISC to serve as the antisense guide strand
- The guide strand then binds to the relevant sequence region of the target mRNA and induces cleavage of the target mRNA
- The cleaved mRNA is degraded, and its gene is “silenced”



siRNA

Market Cap: $4,300 M
Dominant Technology: siRNA

NASDAQ: ALNY

Development Programs:

- **TTR Amyloidosis**
  (Orphan disease)
- **Hemophilia**
- **Acute Intermittent Porphyria**
- **Hypercholesterolemia**
- **Complement-Mediated Diseases**
- **Beta-thalassemia and Iron-overload disorders**
- **Alpha-1-Antitrypsin Deficiency**
- **Liver Cancers**
- **RSV Infection**

siRNA

Market Cap: $745 M
Dominant Technology: siRNA

NASDAQ: ARWR

Development Programs:

- siRNA for hepatitis B (PI)
- Liver target
- Extra-hepatic

siRNA

Market Cap: $468 M

Dominant Technology: LNP for siRNA delivery

NASDAQ: TKMR

Development Programs:

- siRNA for Ebola virus
- siRNA for cancer (PLK1) (PII)
- siRNA for hepatitis B
- siRNA for Alcohol Use Disorder

siRNA

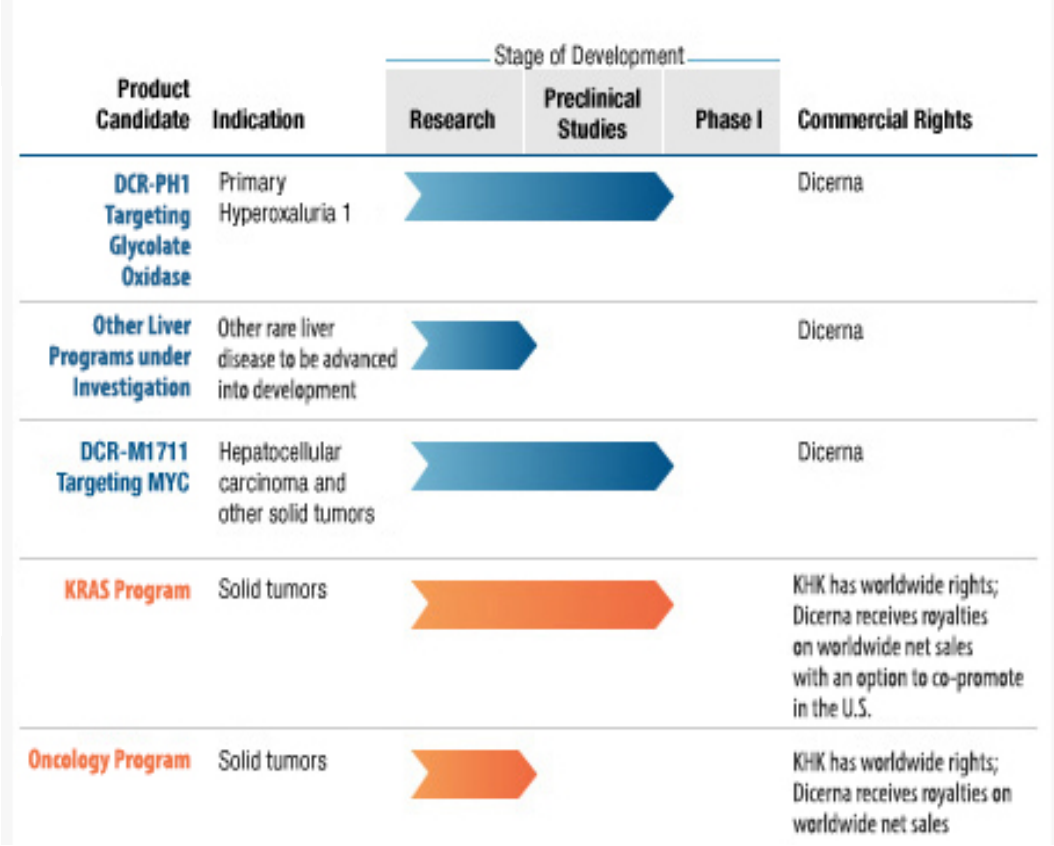
Market Cap: $501 M

Jan 29, 2013: Dicerna priced its IPO at $15 a share. The shares opened on the Nasdaq at $30 and closed at $46 a share!

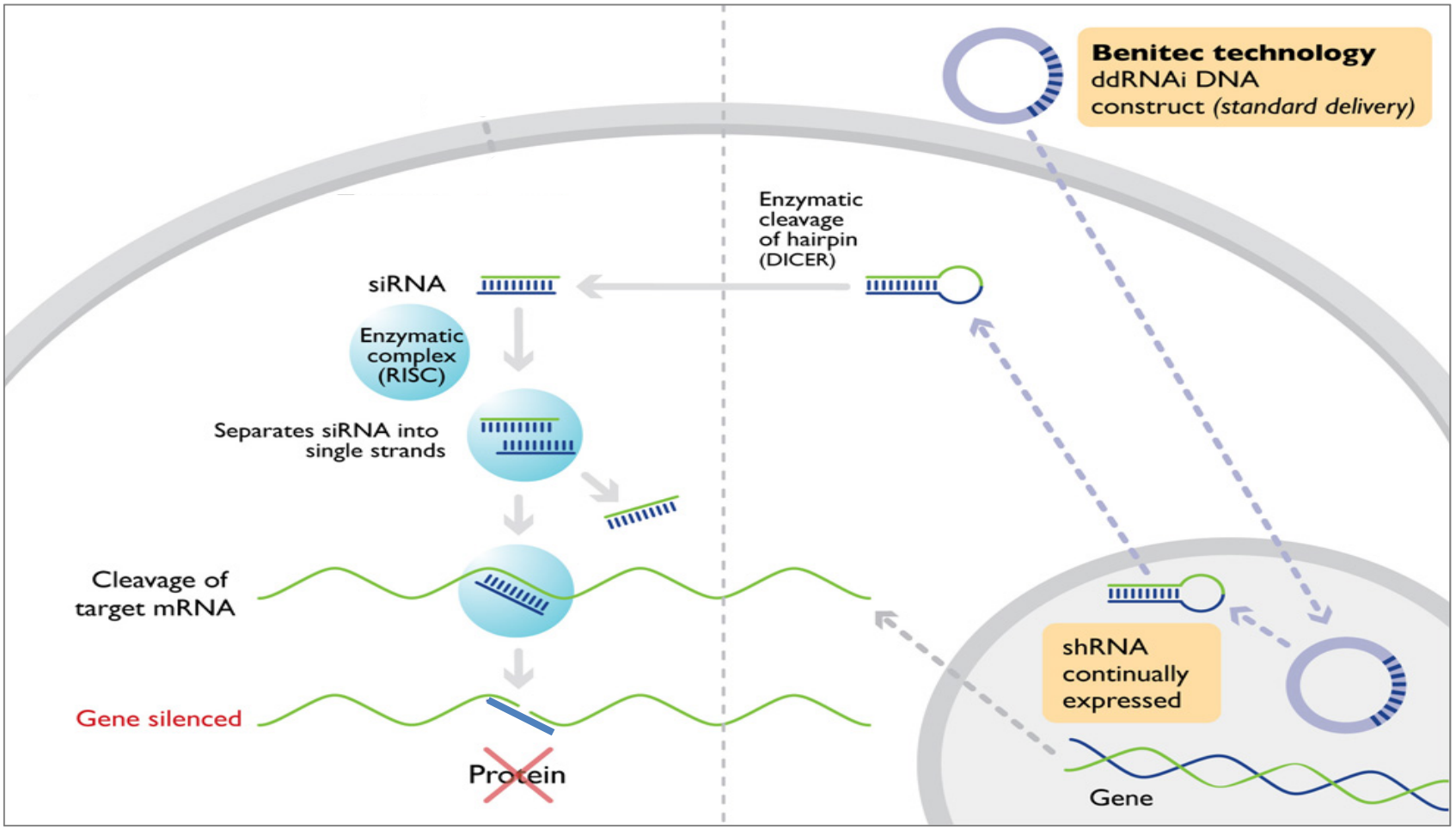
NASDAQ: DRNA

Dominant Technology: DsiRNA

Direct Targeted DsiRNAs™: DsiRNAs are covalently conjugated to delivery agents, thereby eliminating the need for lipid nanoparticles. This system, which is still being optimized, holds the promise of generalized delivery of DsiRNAs to nearly any cell type in the body.

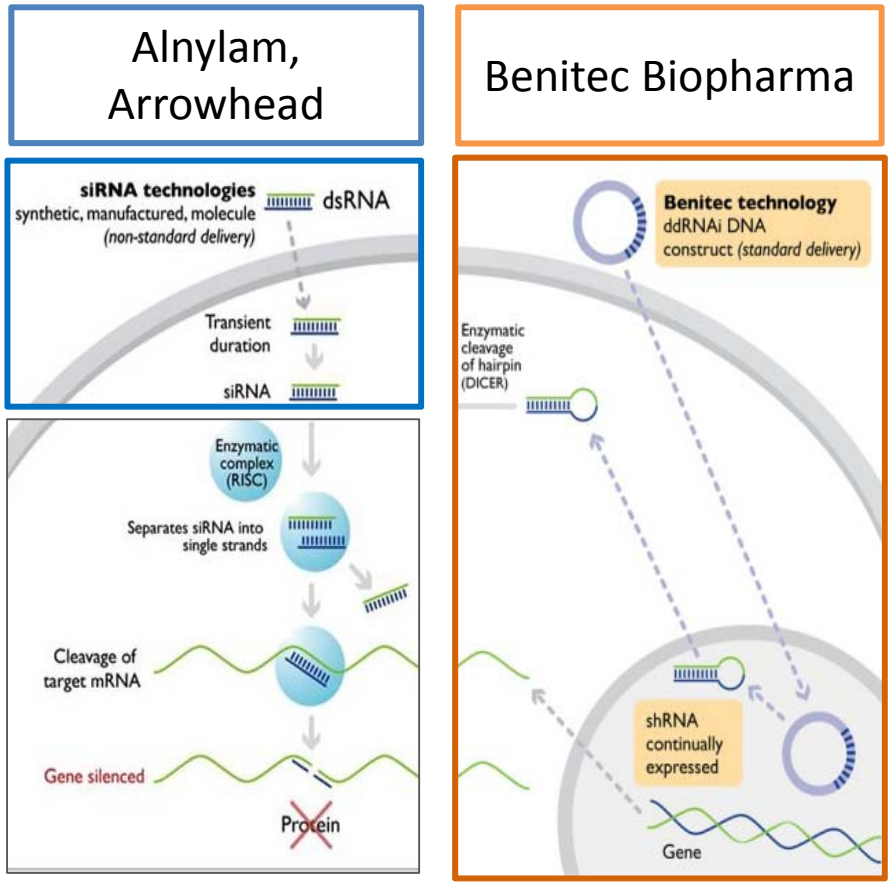


ddRNAi



ddRNAi

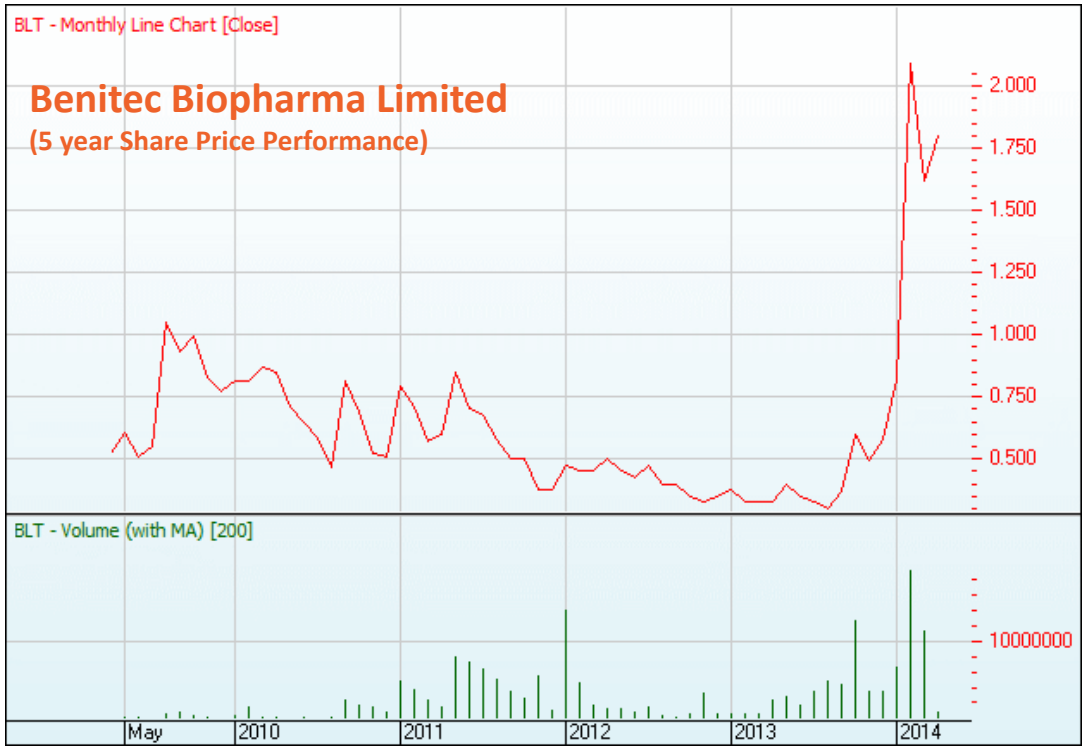
- **A specific and long lasting method for turning off disease-associated genes**
- **ddRNAi technology utilises the power and specificity of RNAi while avoiding many of its problems**
  - **Specific** delivery to target cells
  - **Fewer side effects**
  - **Lasting benefits** – dsRNA generated continuously for the life of the cell
  - **Multiple therapy in a single molecule** – can be engineered to silence a specific gene, multiple sites on a gene or multiple genes
- **Protected by a dominant, global patent estate - over 100 patents covering ddRNAi and specific disease targets**



ddRNAi

Market Cap: $180 M
Dominant Technology: ddRNAi

ASX: BLT



Development Programs:

- Hepatitis C
- Hepatitis B
- Drug-resistant lung cancer
- AMD
- Pain
- OPMD

24th February - announced AUD$31.5M capital raise to US institutional investors

* Reflects post consolidation data

Hepatitis C: TT-034

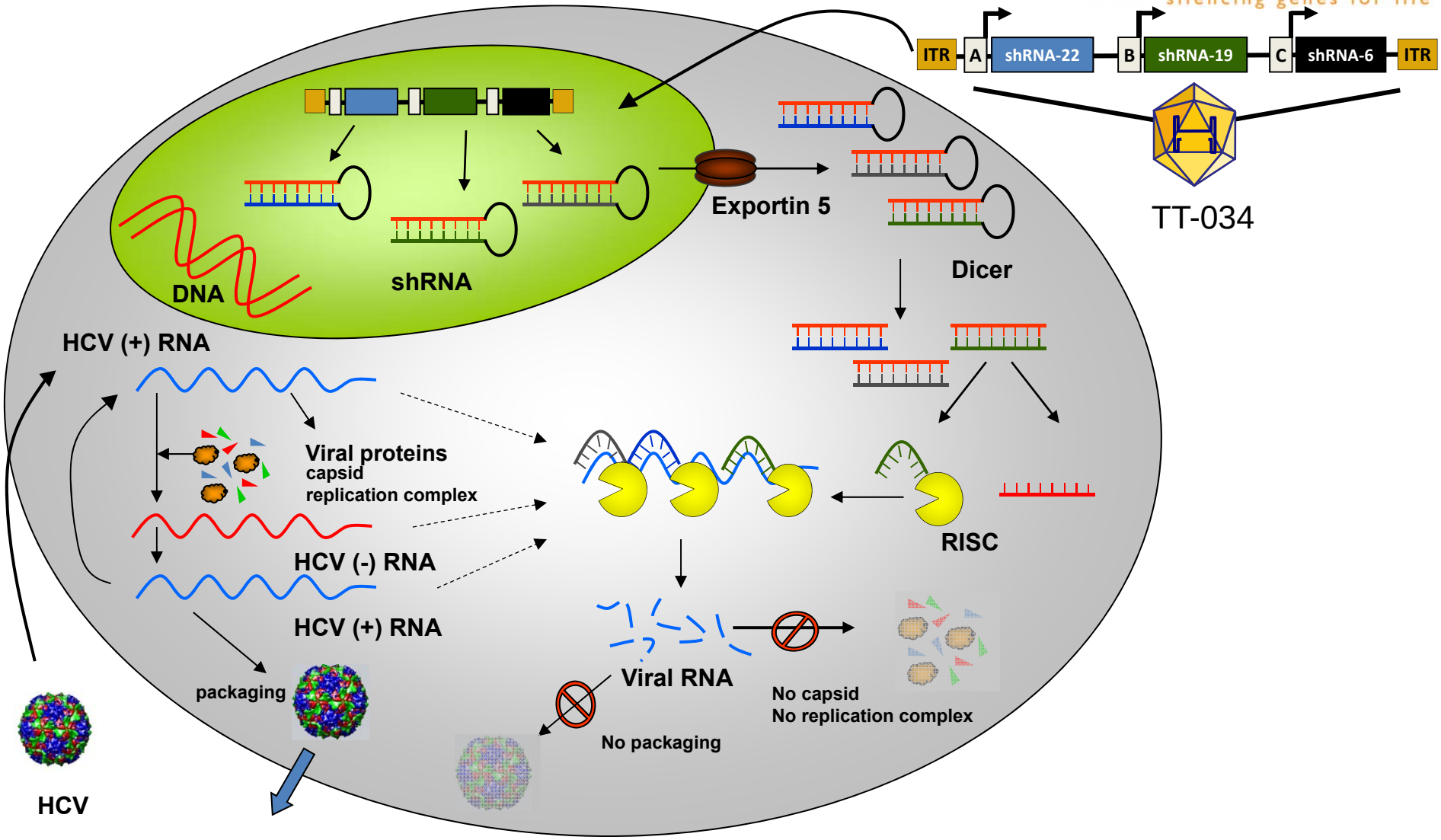
- HCV affects over 180 million people worldwide[1]
- 1 in 100 Americans infected[2]
- Anticipated to be a $20 billion therapeutic market by 2020[1]

- **TT-034 is an RNAi therapeutic that is intended to achieve complete elimination of virus with a single infusion**

- **Competitive advantages**
  - shRNA target three separate, well conserved regions of HCV RNA genome
  - Capability for near complete liver transduction
  - Very low toxicity in animal studies
  - Eliminates long treatments and patient compliance issues
  - Potential pricing and compliance would be attractive to healthcare providers

1. Bloomberg.com Media Release 16/10/2012 Available http://www.bloomberg.com/news/2012-10-15/abbott-s-hepatitis-c-drugs-clear-virus-in-99-of-patients.html ; 2. Denniston MM *et al. Ann Intern Med.* 2014;160(5):293-300

MOA of TT-034 Against HCV



Phase I/IIa clinical trial

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	4.00×10^{10}	Starting dose	2	Sequential (1+1)	6 week
2	1.25×10^{11}	0.5	3	Sequential and parallel (1+2)	6 week
3	4.00×10^{11}	0.5	3	Sequential and parallel (1+2)	6 week
4	1.25×10^{12}	0.5	3	Sequential and parallel (1+2)	10 weeks
5	4.00×10^{12}	0.5	3	Sequential and parallel (1+2)	10 weeks

- Two US trial sites – Duke Medical and University California San Diego
- 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

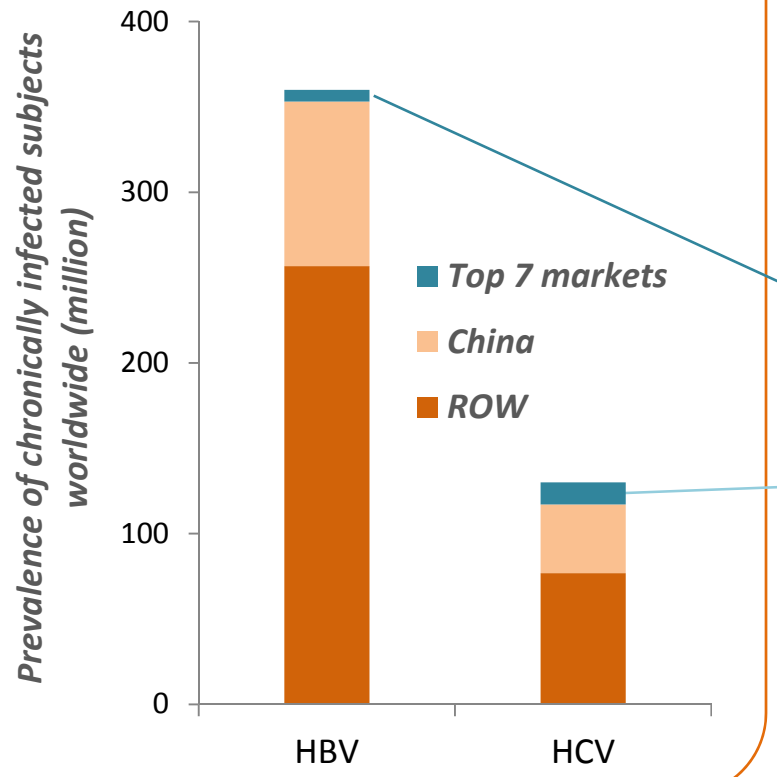
Secondary Endpoints (Efficacy):

- 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 and B viral infections: Significant commercial opportunities

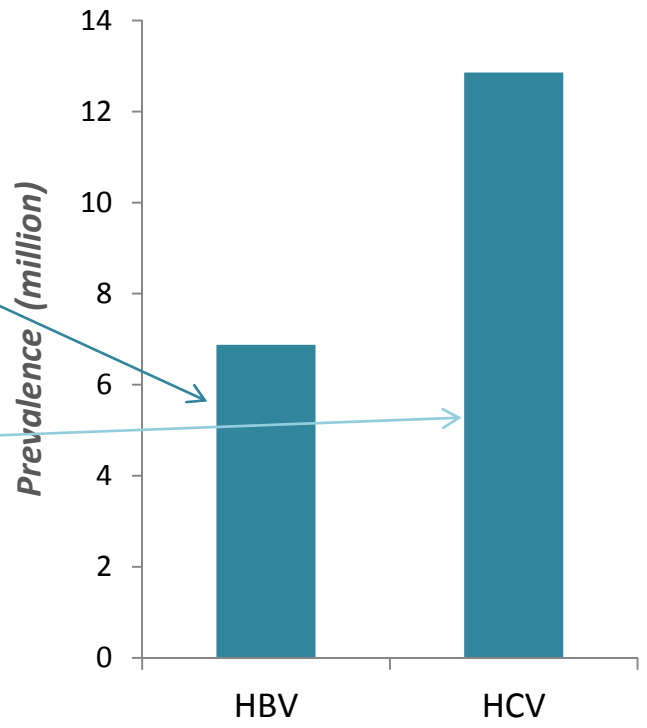
Worldwide, HBV is three times more prevalent than HCV

Chronic HBV and HCV prevalence worldwide



In the top Western markets HCV is twice as more prevalent than HBV

HBV and HCV prevalence in top 7 markets*



*US, EU5 (UK, France, Germany, Italy, Spain), Japan

Sources: Datamonitor 2004, 2007 to 2011. WHO, CDC, IMS, analyst reports

The rationale for RNAi in HBV therapy

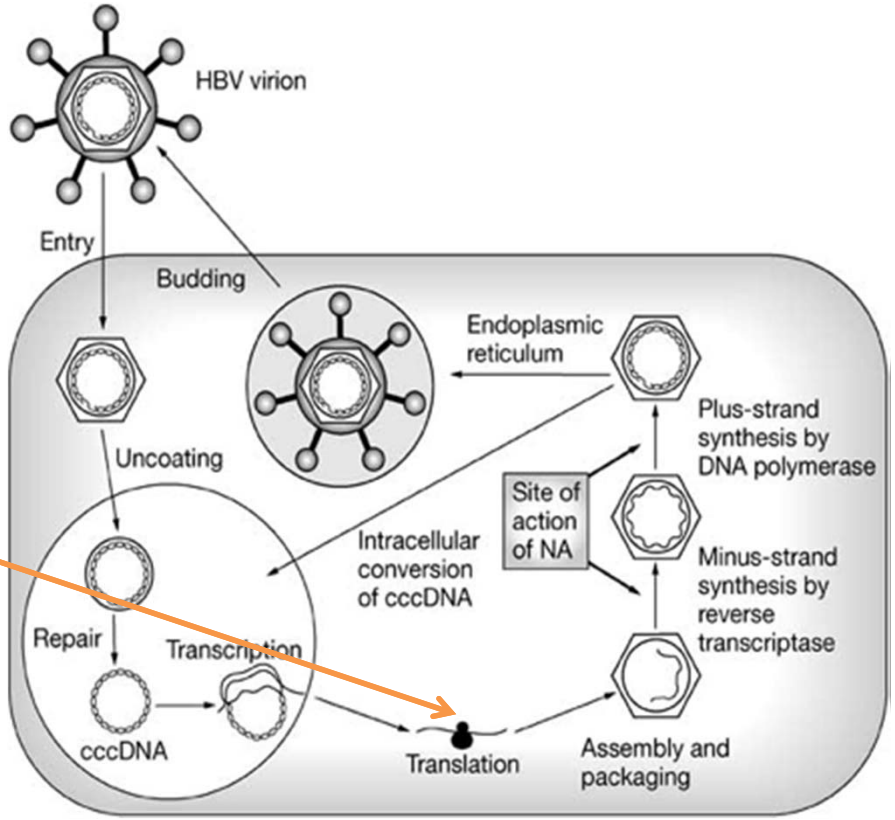
Increased pharma investment and interest in novel antiviral treatment modalities for chronic hepatitis B.

RNAi is one of the most promising.

HBV is susceptible to RNAi because it replicates via an RNA intermediate.

siRNA needs repeated dose.

ddRNAi can provide a single dose treatment to silence HBV mRNA long term.



Drug resistant non-small cell lung cancer

- Lung cancer is the most common cancer worldwide
- The leading cause of cancer-related deaths worldwide (1.3 million deaths p.a.)
- The rapid emergence of drug resistance is a major challenge as it results in high and rapid mortality.

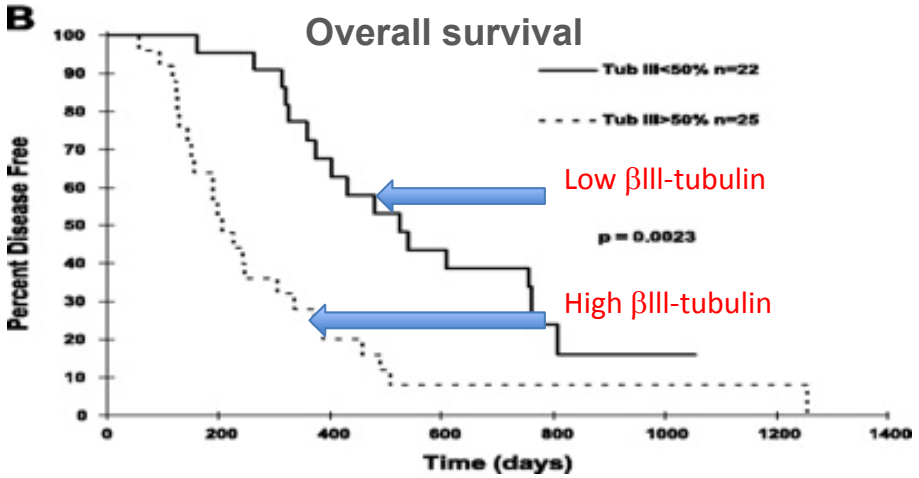
A significant need exists for a therapy capable of restoring and/or improving the effect of therapeutic drugs in resistant tumours

Target gene: βIII-tubulin Rationale

- **Resistance to chemotherapy is strongly associated with over-expression of βIII-tubulin, (encoded by the *TUBB3* gene)**
- **Inactivation of *TUBB3* can restore chemosensitivity**

βIII-tubulin expression in lung tumours is associated with significantly decreased patient survival.

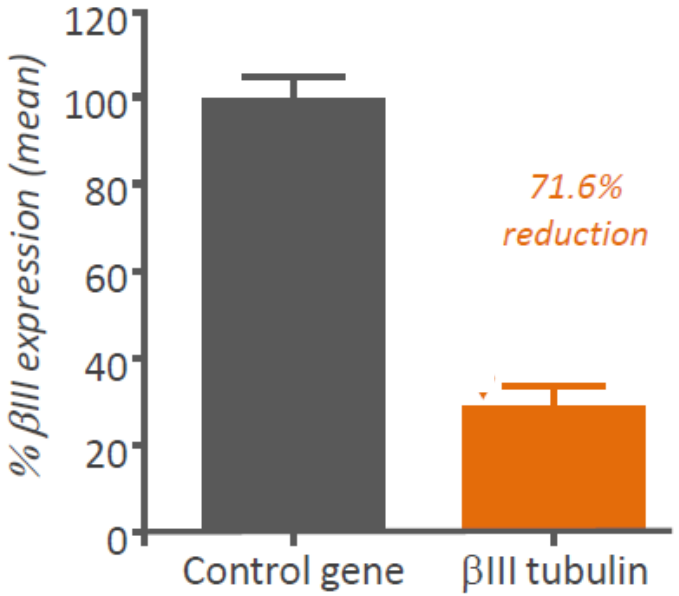
Source: Seve *et al*., 2005. *Mol Cancer Ther.*



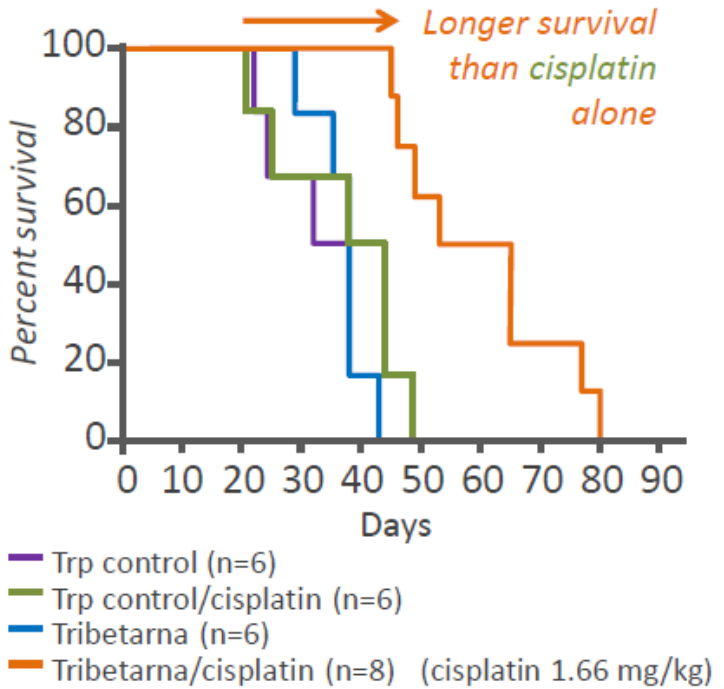
ddRNAi-based therapeutic: Tribetarna™

Proof-of-principle is established:

A single injection of Tribetarna effectively silences the βIII tubulin gene in vivo *and* in vitro



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



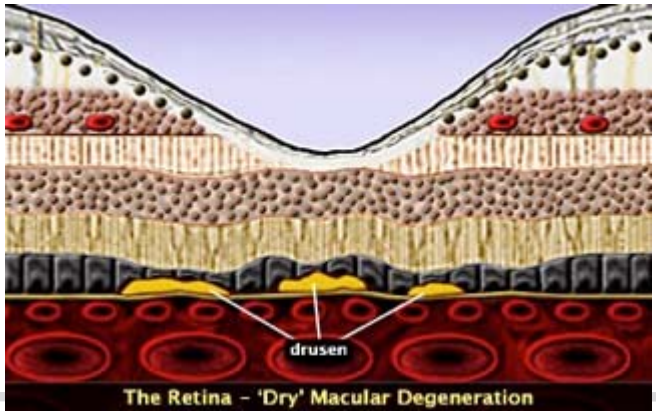
Age-related macular degeneration (AMD)

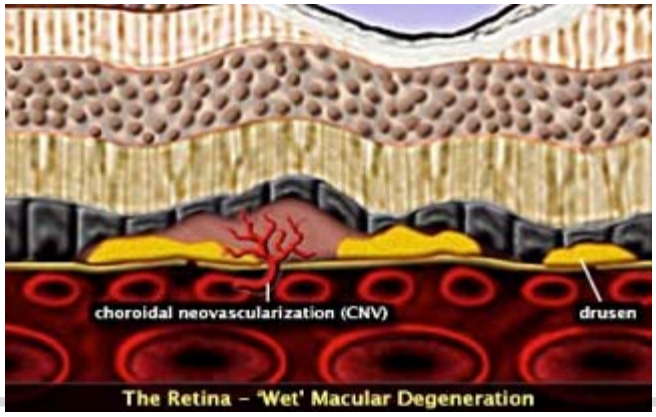
AMD is the leading cause of irreversible vision loss in the US – estimated 1.75M people

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

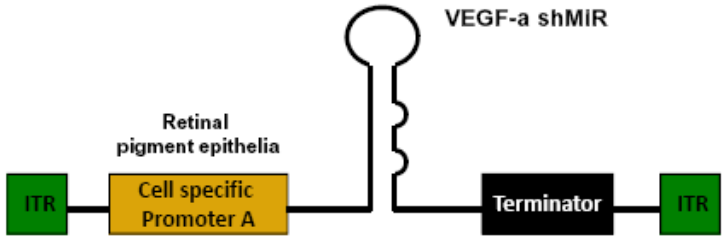
In wet AMD, an inflammatory response sets off a cascade on events that further degrades vision through neovascularisation



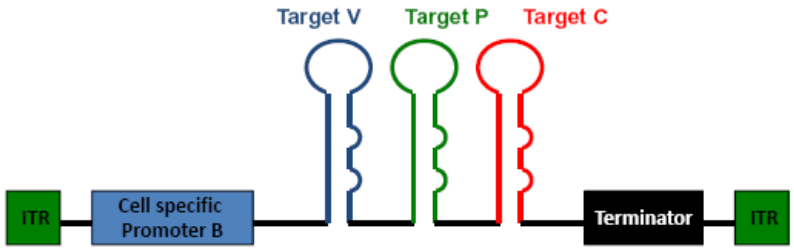


ddRNAi-based AMD therapeutics

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 shRNAs modeled into a miRNA backbone to inhibit the expression of Target V, Target P, and Target C for the treatment of wet and dry AMD



Summary

Securing the recent funding delivers the potential to secure optimal shareholder value:

- ✓ Transforms Benitec Biopharma to a company with multiple clinical assets
- ✓ Allows Benitec Biopharma to take HCV trial to completion of Phase IIb
- ✓ Confirms US-based and international institutional fund support
- ✓ Allows Benitec Biopharma to negotiate from a stronger position with potential partners
- ✓ Will advance all other value adding programs
- ✓ Equips the Company with the resources required to further develop the technology and platform into new areas generating new IP
- ✓ ddRNAi has a bright future

[FAMOUS] LAST WORDS….

The rise and fall and rise of RNAi:

"Do not gloat over me, my enemy! Though I have fallen, I will rise"

Micah 7:8

"The greatest glory in living lies not in never falling, but in rising every time we fall"

Ralph Waldo Emerson, or *Confucius*

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