



# Benitec Ltd (ASX:BLT)

Investor presentation

October 2007

# Investment Highlights

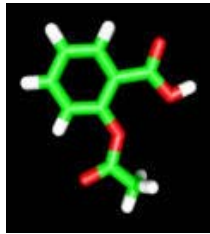
- Strong international, royalty-generating IP position covering seminal patents in DNA-directed RNA interference (ddRNAi)
  - ddRNAi -DNA-delivered RNAi - A DNA 'mini-gene' that is transcribed by the cell into dsRNA, which is then cut into guide RNAs
  - Mimics natural production of dsRNA
  - Introduced into cells with biological vectors
- Focused on commercially attractive, major, life-threatening diseases in cancer and infectious diseases
- Lead product in human trials targeting HIV/AIDS
- Licensing deals and collaborations with industry-leading partners (Sigma Aldrich, Pfizer Inc, Merck Inc, Promega) for research, commercial and therapeutic uses of ddRNAi. Potential for additional ddRNAi and shRNA collaborations
- RNAi field given scientific boost with Nobel Prize awarded to Fire and Mello
- RNAi field given commercial/financial boost with recent deals
  - Merck acquired Sirna for 1.1B in 2006 a premium of around 95% ie 2x market cap
  - Alnylam/Roche non exclusive \$331 million deal 2007 -share price leapt more than 50 percent, from \$15.20 to \$23.12
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**Benitec represents at present valuations an attractive investment opportunity**

# RNAi- The next wave of drug development

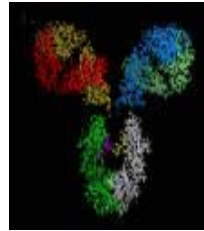


## Small Molecules



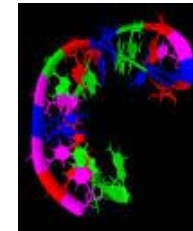
**Target:** Protein  
**Challenge:**  
Specificity  
**Advantage:** Gold  
standard of  
treatment

## Antibodies



**Target:** Protein  
**Challenge:**  
Penetration  
**Advantage:** Market  
acceptance

## RNAi



**Target:** RNA  
**Challenge:** Delivery  
**Advantage:**  
Targets both  
“druggable” & “non-  
druggable” regions of  
disease-causing  
genes

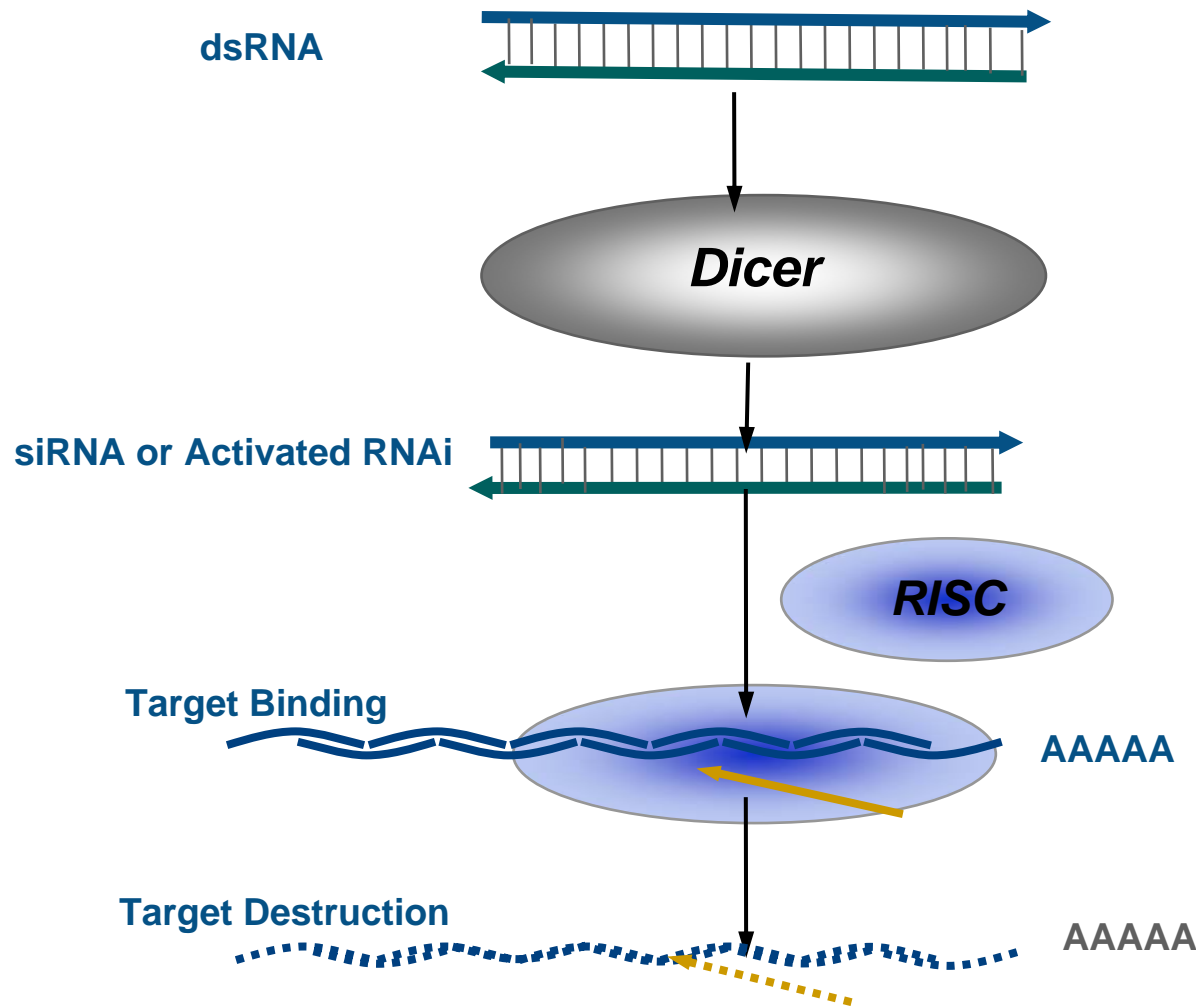
Evolution of drug  
development

“RNA interference (RNAi) represents the most potent mechanism for target specific knockdown of gene expression discovered to date.”

Dr. John Rossi, City of Hope Comprehensive Cancer Center

“RNA interference (RNAi) has revolutionized biology — it has changed the way in which we view gene regulation and is a heaven-sent tool for studies of gene function” Magdalena Skipper (2003), Nature Reviews Genetics 4, 671

# RNAi Mechanism



- Natural mechanism
- Rapidly deployed
- Highly specific
- Catalytic

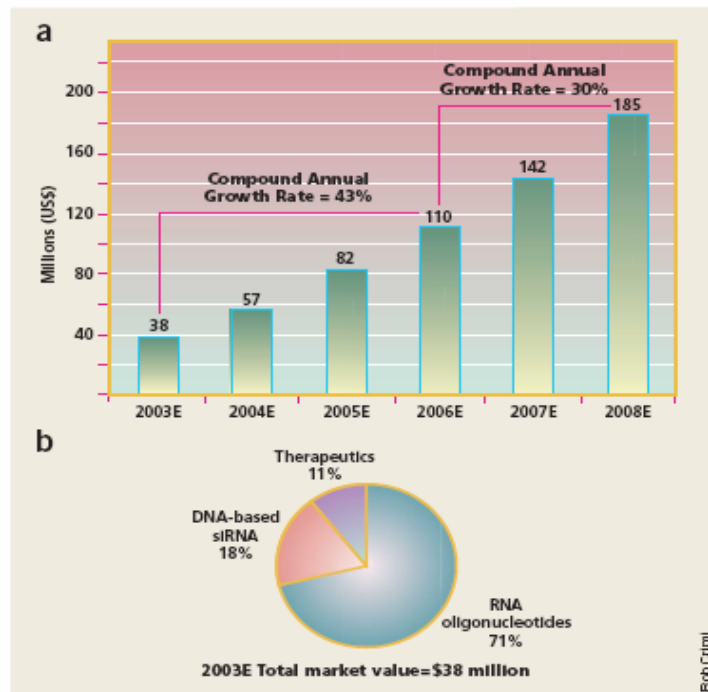
Rapid, highly specific natural established mechanism for gene silencing

# Benitec ddRNAi Advantages

- ddRNAi produces effective gene silencing with a lower dose than siRNA because dsRNA production is effectively catalytic. This attribute may prove critical when targeting infectious agents such as viruses because the virus could potentially replicate so quickly that concentration of a siRNA molecule could become rate-limiting.
- ddRNAi uniquely allows a single payload to target multiple mRNAs. The advantages of multiple drug therapy are well documented and particularly relevant to diseases such as cancers and HIV/AIDS that are characterized by high mutation rates, which inevitably result in the emergence of resistance to single drugs.
- Flexible delivery options - ddRNAi can deliver the construct in a number of ways
  - a plasmid in liposome
  - using viral vectors
  - using stem cells.
- ddRNAi has the ability to be highly targeted to specific tissues allowing for the specific inactivation of key genes in a diseased tissue (this is currently difficult for siRNA)
- Long term gene silencing
- ddRNAi expected to have lower cost of goods and ease of manufacture compared with siRNA because siRNA requires modifications to produce more stable RNA and avoid off target effects.

# RNAi market opportunity

- > US\$1.69 Billion in 2005 RNAi global sales → projected to reach US\$6.65 Billion by 2010 and 12 Billion by 2015 (Therapeutic 1.5B, Research 1.2B, Reagent Use 9.3B)\*
- Competitive and dynamic market

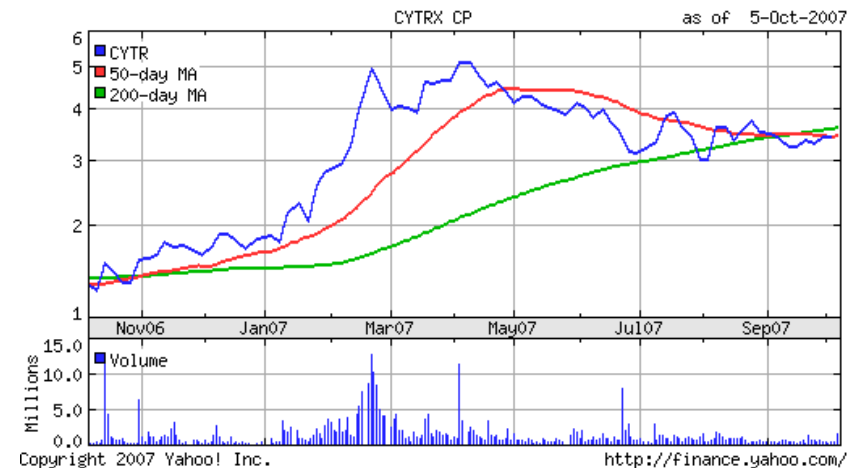
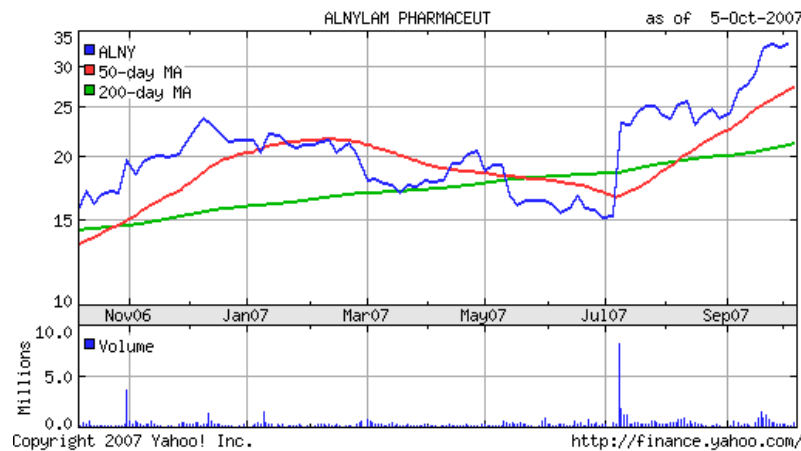


**Figure 1** Estimated annual worldwide revenues from RNAi and market segments. (a) Although the market for RNAi is new and relatively small, rapid growth has been seen and is projected to continue until 2008 as the potential is realized. (b) RNAi market segments. The size of the market reflects the time of adoption—oligonucleotides being the first method employed, followed by vector-based applications. ‘Therapeutics,’ which includes using RNAi for drug discovery, is relatively new. (Figure from ref. 1; courtesy of Front Line Strategic Consulting, San Mateo, CA, USA).



\* RNAi technologies, companies and markets (2006) Jain K.K. Pharmaceutical report)

# Market Reward for RNAi



## Anylam Pharmaceuticals

- IPO \$7 (Jun04) now \$32.85 (Oct07) Market cap - 1.24B
- Roche non exclusive \$US300m RNAi alliance/equity investment deal 2007 -share price leapt more than 50 percent, from \$15.20 to \$23.12
- Novartis 2005 US\$700m R&D collaboration

## Sirna Therapeutics

- Merck 2006 US\$1.2B acquisition - 95% premium

## CytRx

- 5x increase in market cap in 18 months US60M to US300M

**RNAi companies reward investors**

# Dominant International RNAi IP Position

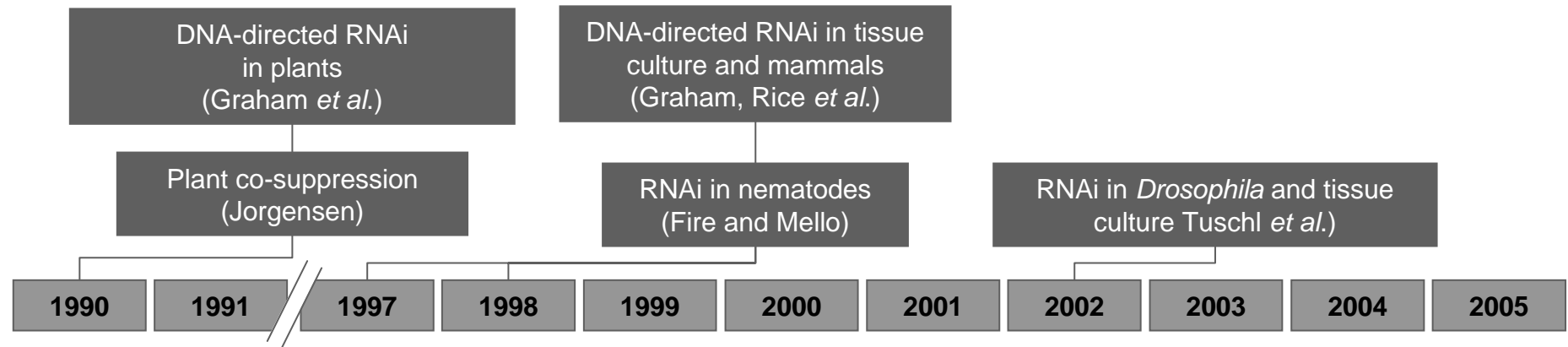
**Benitec was the first company to demonstrate RNAi in human cells and has pioneered ddRNAi and holds a dominant international IP position in RNAi human therapeutics**

*“Most of the IP in (RNAi) is owned by Benitec... Benitec lays claim to a seminal US patent... that describes ‘genetic constructs for delaying or repressing the expression of a target gene’”*

-Nature Biotechnology, *“Negotiating the RNAi patent thicket”*  
(March 2007)

- Core U.S. and U.K. technology patents granted in 2003
  - Cover method for silencing any gene in any cell using ddRNAi
  - World’s first claims describing RNAi effects in human cells and DNA constructs that trigger RNAi
- Published as WO 99/49029.
- Granted: Australia 743316, Canada 2323726, Czech Republic 295108, Great Britain 2353282, Hong Kong 1035742B, New Zealand 506648, Singapore 75542, South Africa 2000/4507, United States 6573099 (under re-exam)
- In Aug 2006 Benitec Australia Limited assigned ownership of these patents to CSIRO and retains a worldwide non-revocable right to all human therapeutic applications

# Core Platform Intellectual Property Rights



Carnegie US 6,506,559  
siRNA in vitro

Benitec US 6,573,099  
ddRNAi *in vitro* and *in vivo*

UMMS/MIT/Max Planck 10/832,248 and 10/832,432 (NoA)  
siRNA in vitro and in vivo (licensed to Sirna and Alnylam)

Benitec  
- additional issued patents  
worldwide including UK, South  
Africa, Singapore, Canada,  
Hong Kong, Australia

ddRNAi *in vitro* and *in vivo*

Sirna US 7,022,828  
siRNA knockdown of IKK-gamma

Discovery

Issued Patent

# Freedom to Operate Supported by Broad Patent estate

## Core Technology

GENETIC CONSTRUCTS FOR DELAYING OR REPRESSING THE EXPRESSION OF A TARGET GENE  
6,573,099 (US) (under reexam)

CONTROL OF GENE EXPRESSION PCT/ AU99/00195, WO99/49029, AU 29163/99, CA 2,323,726, CZ  
PV2000-3346 (295108), GB GB2353282 ,HK 01105904.3, NZ 506648 ,SG 200004917-1, ZA 2000/4507

## Additional Patents

- SYNTHETIC GENES AND CONSTRUCTS
- METHODS AND MEANS FOR OBTAINING MODIFIED PHENOTYPES
- GENETIC SILENCING
- DOUBLE-STRANDED NUCLEIC ACID
- MULTIPLE PROMOTER EXPRESSION CASSETTES FOR SIMULTANEOUS DELIVERY OF RNAI AGENTS
- THERAPEUTIC RNAI AGENTS FOR TREATING RESTENOSIS
- THERAPEUTIC RNAi AGENTS FOR TREATING PSORIASIS
- RNAi AGENTS FOR MAINTENANCE OF STEM CELLS
- METHOD FOR DETECTION AND CHARACTERIZATION OF SHORT NUCLEIC ACIDS
- RNAi EXPRESSION CONSTRUCTS
- RNAi EXPRESSION CONSTRUCTS WITH LIVER-SPECIFIC ENHANCER/PROMOTER
- MULTIPLE RNAi EXPRESSION CASSETTES FOR SIMULTANEOUS DELIVERY OF RNAi AGENTS RELATED TO HETEROZYGOTIC EXPRESSION PATTERNS
- EXPRESSION MODULATING AGENTS-II
- DIFFERENTIAL EXPRESSION OF SHORT HAIRPIN RNA BY MUTAGENIZED OR HYBRID RNA POL III PROMOTERS
- MODULATION OF HAIR GROWTH

# Licensees and strategic partners

Licensing deals and collaborations with industry-leading partners  
 Potential for additional ddRNAi and shRNA collaborations

## Therapeutic use of ddRNAi

- Tacere Therapeutics Inc (HCV)
- Alnylam Pharmaceuticals Inc
- CombiMatrix Corp
- Revivicor



## Research reagent or transgenic animal product development and sales

- Sigma-Aldrich Inc
- Chemicon (Millipore)
- genOway
- Artemis Pharmaceuticals
- Promega Corp.
- IDT
- GenScript Corp
- Ambion Inc (Applied Biosystems)
- Origene Technologies Inc



## Research freedom to operate

- Merck Inc
- Pfizer Inc



## Strategic cross-licensing

- Alnylam Pharmaceuticals
- CombiMatrix Corp
- Carnegie Institute





# HIV/AIDS stem cell program



## Molecular targets rHIV7-shI-TAR-CCR5RZ

- HIV genome
- Cell-surface receptor
- Replication machinery
- Vector manufactured by City of Hope's Center for Biomedicine and Genetics, BLT's collaborative partner

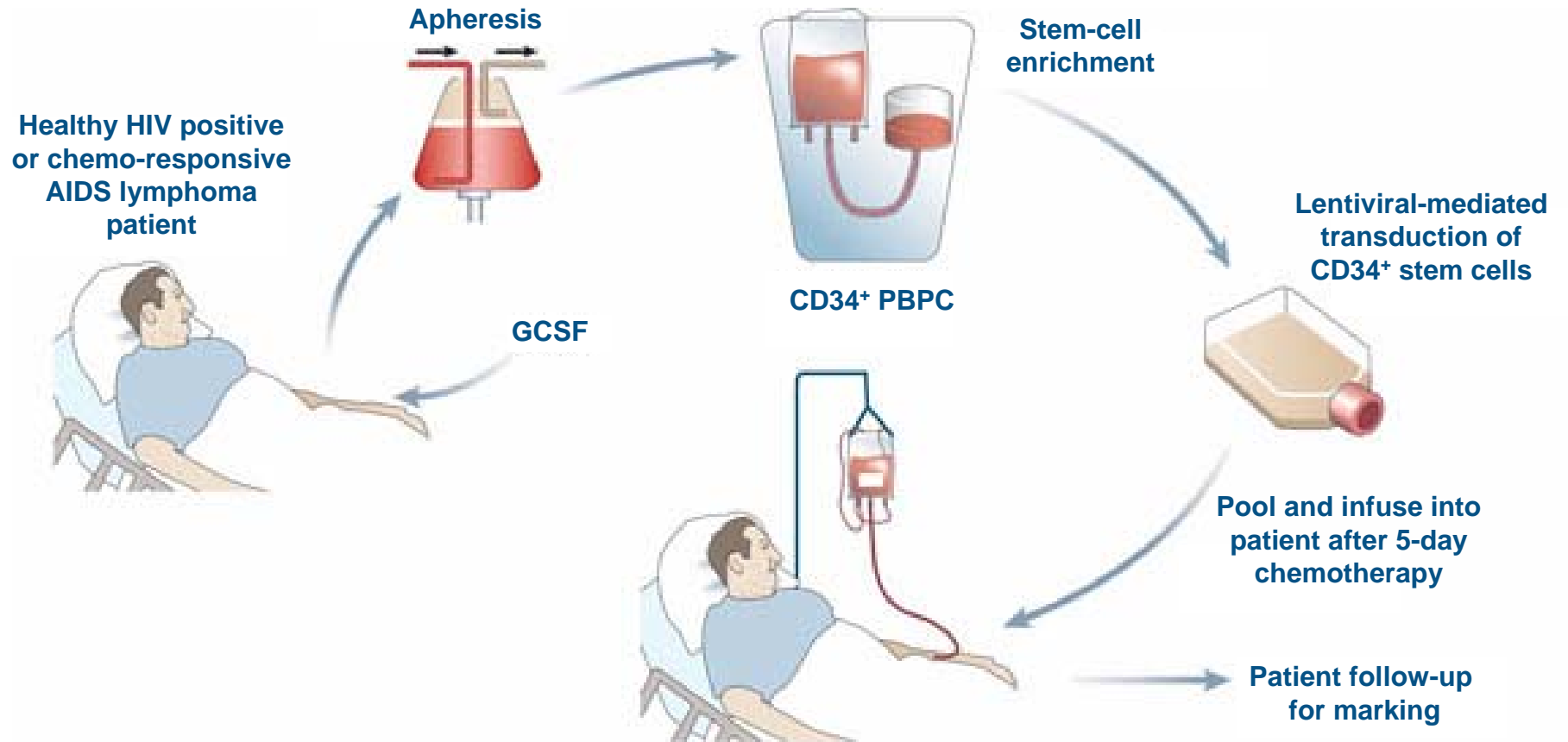
Published in *Nature Reviews*, *PNAS* and *Molecular Therapy*

Undergoing safety and feasibility pilot study evaluating stem cell treatment of AIDS lymphoma using stem cells treated with lentivirus vector-encoding multiple anti-HIV RNA's

## Development milestones

- IND filed (Jan 2007)
- First Human clinical trial commenced in Q307

# AIDS / lymphoma clinical trial design



## T-Cell therapy for HIV/AIDS

- Inclusion of selective marker into clinical vector rHIV7-shI-TAR-CCR5RZ protected >80% of T-cells from HIV infection in macaques
- Collaborative partners: City of Hope, Fred Hutchinson Cancer Research Center, Colorado State University and U Penn
- US\$7.5 million NIH grant covering development through end of Phase I

## Development Milestones

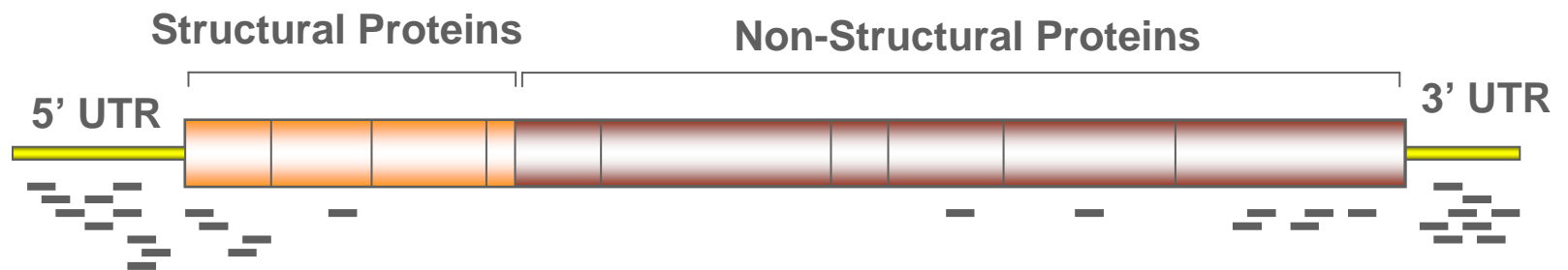
- Pre-IND meeting held Feb 2007
- IND submission expected late 2007
- Phase I initiation in Q1/Q2 2008

Licensed to Tacere Therapeutics Inc.

RNAi Therapeutics targeting Hepatitis C virus genome

- Multi-targeting to prevent viral escape
- Single drug “Cocktail”

Results published in *Nature* and *Nature Biotech*



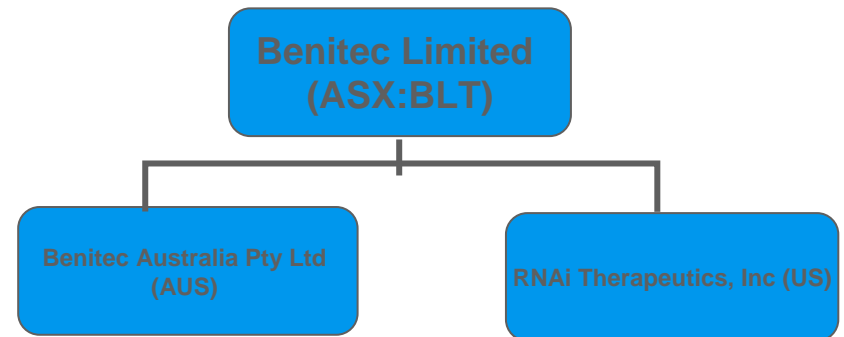
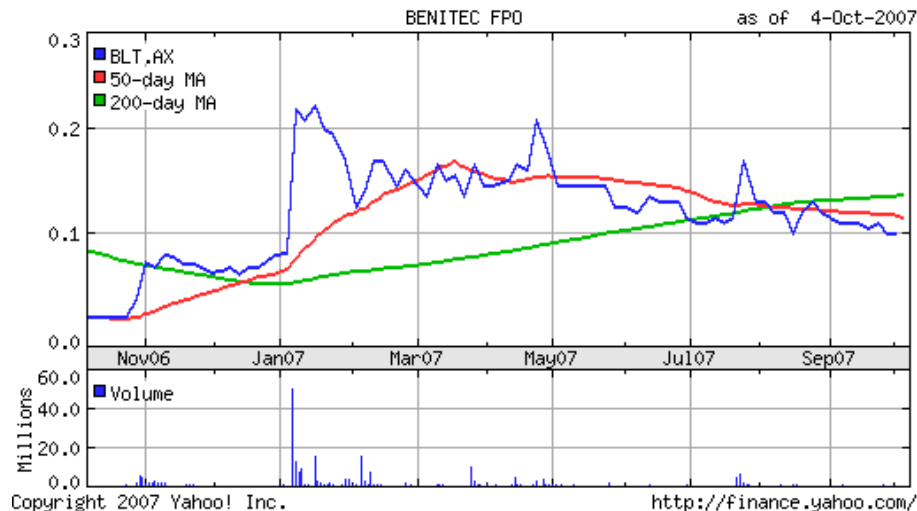
- Further develop proprietary position for Benitec in infectious diseases and cancer
- Strengthen IP underpinning partnerships, collaborations and potential merger and acquisition activities
  - Continue to prosecute core patent claims globally (USPTO re-exam)
  - Patent prosecution and maintenance on supporting IP Increase therapeutic licenses for non-core areas
- Assist current licensees to increase product revenue
- Continually consider Trade sale and exit opportunities

## Benitec capital structure

Approximately 2,621 shareholders  
 Board & management hold <2%  
 Top 20 holders represent 65.86% of issued capital  
 Key shareholders include:

- Dr. Christopher Bremner	19.09%
-Artemis (Rothschild Family)	8.53%
- Sigma Aldrich	6.77%
-Thorney Investments	5.89%
-Promega Corp	6.15%

<b>Share price</b>	\$0.1250* per share
<b>L12M H</b>	\$0.2639 per share
<b>L12M L</b>	\$0.0197 per share
<b>MV:</b>	\$36.05 million*
<b>Issued equity:</b>	288,431,353
<b>Options:</b>	111,362,631
<b>Cash position:</b>	\$4.960 million (30 June 07)
<b>Years:</b>	6-8 quarters
<b>Liquidity:</b>	1,182,938 shares/day
<b>Convertibles:</b>	\$52,980: Chris Bremner



New capital structure to be in place in 2008. Benitec Inc, Benitec LLC and Benitec Limited UK to be incorporated into Benitec Limited  
 \* As at 5<sup>th</sup> October 2007

# Board, SAB and senior managers

## **Peter Francis – Chairman**

Boron Molecular P/L, Xceed Biotechnology, PolyNovo Biomaterials P/L

## **Dr Ken Reed – Director**

QABC, Advanced Breeding Tech P/L, Australian Biotech Advisory Council, Australian Government's Genetic Manipulation Advisory Committee & Australian Genome Research Facility.

## **Dr Michael Dalling - Director**

Biomedical Imaging Development CRC, Biomass Conversion Technologies P/L, Neural Diagnostics P/L, General Division of the Order of Australia

## **Sue MacLeman – CEO and MD**

Schering Plough, Amgen, Bristol Myers Squibb Pharmaceuticals, Agenix Ltd, EQiTX Ltd, Australia Institute of Company Directors, AusBiotech Limited, PIWG, PIC, PIDT

## **John Rawling – CFO, Company Secretary**

Polynovo Biomaterials Pty Limited, EQiTX Ltd, Kentor Gold Ltd, Terrain Australia Ltd, Online Trading Systems Ltd., Australian Grand Prix Corporation.

## **Dr Jason Smythe – CSO**

NH&MRC C.J. Martin Fellow and then an Irvington Institute (New York USA) ,Postdoctoral Fellow in Immunology (Dr Robert C. Gallo lab), National Cancer Institute USA, Johnson & Johnson Research, Gene Therapy Research Unit at the Children's Medical Research Institute (CMRI), Westmead, CSIRO Division of Molecular Science Chief Scientific Officer of the Australian Tissue Engineering Centre Limited in Melbourne.

## **Scientific Advisory Board**

Dr John Rossi – City of Hope Duarte California USA

Dr Bryan Williams – Monash Medical Research Centre – Victoria, Australia

Dr Cy Stein – Albert Einstein College of Medicine NYC USA

Dr David Crump – PD&C consultant Australia

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# Thank you

**Sue MacLeman**

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