

Benitec Limited

BLT

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Benitec's Patents Represent the Core Value of the Company

Recommendation Speculative Buy for the High Risk Tolerant Investor

RNAi Intellectual Property Land Grab Underway

Focusing on monetising and exploiting its patent estate through licensing, Benitec has the strongest proprietary position in the Cellular Expressed Double Stranded Ribonucleic Acid Interference (ddRNAi) sector.

RNAi is a new discovered and relatively unproven technology. There remains uncertainty over the intellectual property covering the sector; yet pharmaceutical companies are actively pursuing RNAi-based therapeutics. This is demonstrated by the acquisition of Sirna by Merck, the licensing deals signed between Alnylam/Roche and Silence Therapeutics/Astra Zeneca; as well as the Research Use License acquired by Pfizer and Merck for Benitec's ddRNAi technology.

Benitec's Patents represent the Core Value Proposition

- Benitec's IP describes expression of siRNA in the cell. This is a valuable suite of IP to own, because the key disadvantage of synthetic RNAi produced by the other main players is deliverability.
- Benitec's core competitive advantage relates to delivery of siRNA. This enabling technology has the potential to rectify the existing drug-delivery bottleneck in the RNAi sector.
- Because of the value of the core patent, a competitor (Nucleonics) has requested the US Patent Office (USPTO) to re-examine the key patent (US 6,573,099 or '099'), plus this competitor has launched two unsuccessful appeals in the US courts.
- As the patent is in review, the key risk for Benitec is whether (or how) the USPTO may amend the patent.

Recommendation

Benitec is a high risk investment opportunity for investors knowledgeable and tolerant of the investment risks associated with an early stage biotechnology company.

Benitec's key assets are its patents, which are the seminal patents on cellular ddRNAi expression. And as these patents control ownership over ddRNAi expression, Nucleonics has constantly and persistently challenged the validity of '099'.

Therefore, the value in Benitec is wholly and totally reliant upon the outcome of the USPTO's re-examination of its core patent.

- Success with the USPTO will mean that any company seeking to develop an RNAi expression system for research or clinical use must acquire a license from Benitec prior to commercialisation of their product
- Failure with the USPTO will mean that Benitec's core value is extinguished.

It is too early to place a valuation upon the company because of the early stage nature of its drug development programmes and uncertainty over the IP. Nevertheless based on comparable companies, we are confident that the likelihood of Benitec being acquired and new license deals signed increases if Nucleonics' challenge is unsuccessful.

The company is a Speculative Buy for the high risk tolerant investor or a company seeking a controlling stake in ddRNAi cellular expression.

Snapshot

Last Price	\$0.14
Market Cap (m)	\$40.1
52 Week High	\$0.43
52 Week Low	\$0.02
Sector	Pharmaceuticals & Biotechnology

Investment Fundamentals

Year-end June	FY05A	HY06A	FY06A	HY07A
NPAT (\$m)	-14.6	-3.9	-7.7	-0.8
EPS (c)	-14.7	-2.5	-4.7	-0.5
% Change	NA	NA	NA	NA
DPS (c)	NA	NA	NA	NA
Franking (%)	NA	NA	NA	NA
Yield (%)	NA	NA	NA	NA
PER (x)	NA	NA	NA	NA

Source: Intersuisse Estimates

Price Chart



Business Description

Benitec is focused on licensing its extensive intellectual property portfolio (which stem from '099') and developing therapeutics to treat serious diseases using its proprietary ddRNAi technology. Its current therapeutic program is focused on Human Immunodeficiency Virus (HIV). Benitec's RNA-based HIV therapeutic, co-developed with the Centre for Biomedicine & Genetics at the City of Hope (Los Angeles), commenced Phase I clinical trials in June 2007

Analyst: Darren J. Grubb PhD MBA GDipAppFin

The RNAi, siRNA and ddRNAi Intellectual Property Landscape

Similar to the Oklahoma Land Rush of 1889 that defined the US frontier; there is a land grab for the control of the gene silencing sector that will ultimately allow the main players to control this emerging therapeutic area. Gene Silencing is a new technology. Discovered in the 1990's, gene silencing has the potential to allow development of radically new therapeutics that could target diseases in ways not possible using antibodies, biologics, vaccines or chemicals. For this reason, there is strong international interest in gene silencing. Pharmaceutical companies are paying premium dollar to acquire, or gain access to licenses, to the seminal patents that would give drug manufacturers a strong first mover advantage and controlling position.

There are eight seminal patents in the gene silencing sector, being;

Patent	Patent number	Status	Date	Owner	Licensees	Coverage
Fire and Mellow	US 6,506,559	Issued	January, 2004	Carnegie Institute of Washington	Unrestricted	Inhibition of target genes with double-stranded RNA 25 nucleotides or more in length.
Tuschl et al. (Tuschl I)	US 108,923	Application pending	NA	UMass Medical School, MIT, Whitehead Institute, Max Planck Institute	Alylam, Sirna, Cytrx	Inhibition of target genes with double-stranded RNA between 21 and 23 nucleotides in length. Includes overhangs, chemical modifications and data from mammalian cells.
Tuschl et al. (Tuschl II)	US 7,056, 704	Issued	June, 2006	Max Planck Institute	Alylam	Short RNA fragments 19-23 nucleotides in length are sequence-specific mediators of RNAi in <i>Drosophila melanogaster</i> . Describes 3' overhangs.
Tuschl et al. (Tuschl III)	US 7,078, 196	Issued	July, 2006	Max Planck Institute	Alylam	Second patent in Tuschl II series. Describes in greater detail the use of siRNA in mammalian cells.

Kreutzer-Limmer	EP 1,144,623	Issued	2002	Benitec	Not available	Describes RNAi in molecules from 15 to 21 nucleotides in length. Provides coverage in Europe, Australia and South Africa.
	US 6,573,099	Issued then pulled for reexamination	June, 2003 (issuance date)	Benitec	Not available	Genetic constructs for delaying or repressing target gene using expressed system.
	US 5,898,221	Issued	April, 1999	Crooke	Alylam	Chemical modifications to stabilize RNA.
	US 6,107,094	Issued	April, 2000	Crooke	Alylam	Chemical modifications to stabilize RNA.

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Benitec's IP Position

Benitec has a strong IP position, although as mentioned, Nucleonics' request to have the Benitec patent '099' re-examined by the USPTO has increased uncertainty over Benitec's IP position.

The key to '099' is its teaching of the use of genetic constructs to allow expression of ddRNAi in mammalian cells. This is a first in class patent, as it describes the ability and utility of RNAi expressed within the cell that could be used for delivery of siRNA.

Other companies have seminal patents in the area that teach the use of synthetic RNAi, which has to be manufactured outside the cell and administered via conventional drug routes.

The differentiating feature of Benitec's IP is that it allows the expression of siRNA in the cell. Viral or nonviral expression vectors transfected into autologous or allogeneous cells have the potential of allowing researchers to circumvent RNAi administration via conventional drug routes. This is a valuable suite of IP to own, because the key disadvantage of RNAi is the issue of deliverability. In addition, synthetic RNAi requires chemical modification¹ to remain stable and

¹ ISIS claims ownership over the 2'-O- methyl chemical modification of RNAi to increase stability and the IP was subsequently licensed to Alylam. This modification allows RNAi to be administered systemically because the modification

delivered with protective agents to allow penetration into the cell.

Although Benitec's technology has the hypothetical potential of increasing some tumours or teratoma, Benitec's use of a benign viral vector reduces the risk of this occurrence.

The Status of '099'

099's Re-Examination History Summary

On 4 October 2004, Nucleonics appointed a third party to re-examination '099', providing the USPTO with prior art it believed invalidated the patent.

The USPTO rejected the claims based on the provided prior art. Benitec overcame the references and the USPTO withdrew all rejections but instituted new rejections on additional prior art it had uncovered.

Nucleonics then requested a second re-examination, adding prior art it believed invalidated '099'. The USPTO merged the two re-examinations and recently sent out an Office Action to Benitec.

On 1 February 2007, the USPTO issued Benitec with a rejection notice for all the claims made in '099'. This meant that the USPTO gave Benitec's attorneys six months to justify the claims to the USPTO.

Benitec made its first counter submission to the USPTO on the 26th April 2007.

Benitec now awaits the USPTO's decision on the acceptance and rejection of claims.

Benitec's IP estate impacts many developers of RNAi therapeutics and Benitec has challenged the competition. It was unhelpful for the company that previous management was more focused on the litigation route instead of the licensing route to enforce its ownership claims. This strategy resulted in a high cash burn. It also distracted focus away from the more commercially lucrative licensing strategy that increases amicability amongst existing and potential partners. The licensing strategy had the potential to accelerate rate of development in the industry using Benitec's technology.

Most patent infringers settled in March 2004 after the US District Court (Delaware) upheld Benitec's ownership of '099'. Yet in October 2004, Nucleonics requested the USPTO to re-examine '099'. Examination of this patent continues.

Nucleonics has been relatively unsuccessful in its attempts to reject or amend the core teachings of '099', although the dispute continues. Nucleonics is very aggressive in challenging Benitec's patents because it prevents Nucleonics from gaining market through sub-licensing its technology, decreases the probability of a trade sale and reduces the commercial returns from development of its

conveys protection against host nuclease activity. The claim on the ownership has not been challenged in the US courts. We notice that 2'-O- methyl modification of RNA to confer nuclease protection was previously reported in 1988 by the Japanese researchers Mukai, Shibahara and Morisawa: *Nucleic Acids Symp Ser.* 1988;(19):117-20

antiviral programmes as royalties and fees would be payable to Benitec.

The status of '099' is a binary risk for the company. We believe that the probability is high of Benitec maintaining most, or all, of its important claims in ddRNAi. Although there is not guarantee of this occurring.

In addition to the patent re-examination, Nucleonics has taken Benitec to court to appeal against its infringement of '099'. After Benitec initiated legal action against Nucleonics and was successful, Nucleonics appealed to the Court of Appeals for the Federal Circuit.

In July 2007, the court ruled 2/1 in favour of the plaintiff stating that...*Nucleonics has not made a showing of "sufficient immediacy and reality" to support declaratory judgment jurisdiction. The district court's judgment of dismissal for lack of jurisdiction is affirmed².*

Basing the precedent of *MedImmune v Genentech*³, the Court of Appeals decided, in part, that there was no case when a party has not yet breached another's patent(s). However, the dissenting Judge believed that there was controversy. The reason being that though there is no controversy now; there would be controversy if Nucleonics develops a human therapeutics. This could result in Benitec and Nucleonics returning to court to establish the issue of patent validity.

Nucleonics can appeal to the Full Bench of the Federal Court, this could only occur if Nucleonics' VC investors provide additional funds solely for the purpose of the appeal given Nucleonics estimated cash position⁴. In addition, the company must be granted leave to apply to the Court to hear the appeal.

However if the appeal is successful Nucleonics could challenge the validity of '099'.

In the event Nucleonics' further appeals the case and is unsuccessful, Nucleonics could rely upon *Merck v. Integra*⁵ which provided a precedent for the use of a patent without obtaining a license for research as long as the infringer is developing a drug for FDA approval and no revenue is being generated by the research.

One of the key risks for Benitec is the financial capabilities of the investors into Nucleonics, being Anthem Capital Management, Burrill & Company, HealthCap Venture Capital, New Enterprise Associates, Paul D. Sonz Partners, POSCO BioVentures, Quaker BioVentures, S.R. One

² United States Court of Appeals for the Federal Circuit (06-1122) BENITEC AUSTRALIA, LTD., Plaintiff- Appellee, v. NUCLEONICS, INC., Defendant-

³ United States Supreme Court Case (05-608) MEDIMMUNE, INC. v. GENENTECH, INC ET AL

⁴ Nucleonics raised US\$49.2m in a Series B funding round in early 2004, but we believe that much of the capital has been spent of its preclinical programmes

⁵ Supreme Court of the United States (03-1237) MERCK KGAA v. INTEGRA LIFESCIENCES, LTD., ET AL

Limited and SK BioPharmaceuticals We do not know the intentions of these investors, but the decision to challenge Benitec's patents would have been supported by Nucleonics' board which includes;

- James Barrett (General Partner - New Enterprise Associates),
- Rajeev Dadoo (Principal - SR One),
- Giovanni Ferrara (Managing Director - Burrill & Company) and
- Per Samuelsson (Partner - HealthCap Venture Capital).

These funds have a strong financial interest in diluting Benitec's position because it currently hinders Nucleonics' ability to sign partnering agreements, license their technology to commercial partners and attract a trade sale. Currently, Nucleonics only has research collaborations with medical institutions.

The General IP Position for Market Players

Due to the various proprietary technology ownerships in the area, most companies have to take out some license(s) from the main players in the sector. The Fire and Mellow 6,505,559 patent (559) has been licensed by most companies, including Benitec. The two Tuschl *et al* patents are also critical to allow freedom to operate in the area. The Tuschl I 108,923 pending patent (923) and the Tuschl II 7,056,704 & 7,078,196 patents (704 & 196) are also central as these teach uses of RNAi between 19-23 nucleotides in length, which is the length required to evade the immune system. Above 23 nucleotides in length, the immune system can mistake RNAi as a viral infection and mount an immune response. Alnylam has the exclusive license for 704 & 196; as well as non exclusive access to 923. Benitec has a licensing agreement with Alnylam, providing freedom to operate.

With access to these seminal patents Alnylam is becoming the central player in the RNAi sector. Alnylam's superiority in the area has allowed it to be granted up to US\$120m⁶ in licensing fees spread over various years and conditional upon product success. Most companies take a license for the Tuschl I and II patents from Alnylam simply to ensure freedom to operate, even though the Tuschl I patent may never be granted by the USPTO.

Alnylam holds about 28 core patents (over 150 issued patents) in the sector and has 10 compounds in preclinical trials and one in Phase I development.

M&A in the RNAi Sector

As with many emerging sectors, pharmaceutical companies are acquiring technologies that would provide them the freedom to operate to undertake R&D, clinical development and commercialisation. The lesson learnt from antibody therapeutics is that the owner of the seminal patents and the technology platform generate licensing and royalty revenues that are often greater than the sale of a drug. Royalty stacking arises when multiple patents affect a single product and are common in the biotech field. The keynote example is therapeutic antibodies, where various royalties and licenses are required to commercialise these antibody therapeutics, particularly those developed using a proprietary technology.

Sirna Acquired by Merck

Sirna Therapeutics was acquired by Merck for US\$1.1bn in October 2006. Sirna was the leading company in terms of core patent estate, owning 81 core patents.

The major patents are

"RNA Interference Mediated Inhibition of Gene Expression Using Chemically Modified Synthetic Short Interfering Nucleic Acid (siRNA)"	Describes the use of chemical modifiers to increase the stability and longevity of siRNA in the body.
"RNA Interference Mediated Inhibition of Vascular Endothelial Growth Factor and Vascular Endothelial Growth Factor Receptor Gene Expression Using Shore Interfering RNA"	Broadly describes the use of siRNA to target viruses and genes that cause disease. Teaches the use of siRNA targeted against the VEGF receptor.
Further patent suites	Further patents broadly describe the uses of siRNA to target RNA viruses and the conserved regions of viruses and genes. These patents cover multiple siRNAs in combination to increase the therapeutic potential.

The acquisition of Sirna complements the research on RNA expression that Merck has been doing since the 2001 acquisition of Rosetta Inpharmatics.

Alnylam Licences Technology to Roche

In July 2007, Alnylam granted Roche a non-exclusive license to RNAi technology for the development of compounds targeting cancer, respiratory, metabolic and liver diseases. Under the deal, Roche provided Alnylam an upfront payment of US\$288.5m and Roche Venture Fund purchased US\$42.5m in shares of Alnylam. At the time of the deal, Alnylam employed 122 employees and reported revenues of US\$26.9m constituting a loss of US\$34.6m

Nastech acquired Galenea RNAi therapeutics programme

In June 2006, Galenea's technology was acquired by Nastech for an undisclosed payment. However, over the life of the deal total payments could reach US\$577m.

⁶ Net revenues from Research Collaborations for the Three Months ending March 2007 was US\$7.2m, contributing to a loss of US\$22m.

The intellectual property acquired from Galenea includes patent applications licensed from MIT that have early priority dates in the antiviral RNAi field. Nastech also acquired Galenea's research and intellectual property relating to pulmonary drug delivery technologies. Additionally, Nastech assumes Galenea's pending grant applications from the National Institute of Allergy and Infectious Diseases (NIH) and the Department of Defense to support the development of RNAi-based antiviral drugs.

Silence Therapeutics deal with Astra Zeneca

In July 2007, Silence Therapeutics signed a deal worth up to £200m with AstraZeneca to develop treatments for respiratory diseases. The three-year collaboration will see the two firms working to develop new treatments against up to five disease targets provided by AstraZeneca, using Silence Therapeutics's RNAi technology.

Silence Therapeutics provided AstraZeneca with a license to the technology for an upfront fee of £7.5m composed of a cash payment of £2.5m and equity investment of £5m. The equity investment was at a 10% premium over the 10 day VWAP giving AstraZeneca 2.94% of Silence Therapeutics.

Competition in the RNAi Therapeutic Development Area

There are various companies develop RNAi-based therapeutics with several in clinical trials. However due to the early nature of this sector, none have progressed past early Phase II human studies. Of the companies undertaking human clinical trials, about one half are developing ddRNAi therapeutics, with the other one half testing synthetic siRNA compounds.

Companies Developing RNAi-based Therapeutics are;

Company	Market Cap	Compounds in clinic (preclinical)
Acuity Pharma*	Private	PII (1)
Alnylam Pharma.	US\$916m	PI (1), PC (11)
Silence Therapeutics	£140m	PI (1), PC (5)
GeneCare	Private	PC(2)
Protiva†	Private	PI(1), PC (5)
Benitec	A\$40.3m	PI (1), PC(1)**
Calando Pharma.	Private	PC (1)
Celladon	Private	PI (1)
CytRx‡	US\$284m	PC (3)
deVGen	€311m	-
Galenea	Private	-
Generex	US\$171m	PI (1)
Intradigm	Private	PC (3)
Nastech	US\$322m	PC (2)
Nucleonics	Private	P1 (1), PC (4)
Santaris	Private	P1 (1), PC (7)
International Therap.	Private	PC (1)
Senesco Tech.	US\$417m	PC (1)
Combimatrix	US\$39m	PC (?)
Oxford BioMedica†	£233m	PC (1)

Sources, Benitec, Yahoo Finance, Company Web Sites

PI = Phase I

PII = Phase II

PC = Preclinical

(n) = The number of programmes underway within a stage of development

*Acuity Pharmaceuticals and Froprix Corporation Agreed to Merge.

‡ RNAi Delivery Technology

‡ In January 2007, CytRx transferred its RNA assets to RXi Pharma. Corp

** Licensed to Tacere Therapeutics Inc

As the field is emerging, Benitec's technology has the opportunity to become the standard for expression of ddRNAi. Additionally, there is limited direct competition to Benitec's expressed ddRNAi technology platform. It is for this reason that '099' is particularly valuable.

We believe that the key end-point that would determine the success of the RNAi-based therapies in clinical development is more validation of the RNAi technology as a therapeutic tool rather than successful treatment of the disease (see Clinical Developments section).

Benitec's Patent Estate

The company has filed over 60 patents and has licenses to several CSIRO patents, all relating to the field of ddRNAi.

Patent protection is expected to continue, as the company further builds its IP estate.

The CSIRO has an undisclosed entitlement to revenues generated in the event of a trade sale of Benitec or licenses signed for use of CSIRO's patents. We believe that the IP ownership structure must become cleaner before a trade sale Benitec could occur. Historically, acquirers desire ownership of the IP and seek to not have to pay sub-licensors in the event of commercial success.

The company's current IP estate includes;

Invention Title	Patent/Application Number
Genetic Constructs For Delaying Or Repressing The Expression Of A Target Gene	6,573,099 (US)
Control Of Gene Expression	PCT/ AU99/00195, (WO99/49029), AU 29163/99, CA 2,323,726, CZ PV2000-3346, GB GB2353282, HK 01105904.3, NZ 506648, SG 200004917-1, ZA 2000/4507
Synthetic Genes And Genetic Constructs Comprising The Same	US 10/821,726, US 11/180,928 , US 11,218,999
Methods And Means For Obtaining Modified Phenotypes	WO99/53050
Genetic Silencing	GB2377221 (GB), P-91678 (SG), 2002/7428 (ZA), AU01/000297, 0170904 (WO)
Double-Stranded Nucleic Acid	10/861191 (US), 2527907 (CA), 04735856.9 (EP), 172191 (IL), 2006/508084 (JP), 200507474-5 (SG), 2005/09813 (ZA), AU04/00075 (WO)
Multiple Promoter Expression Cassettes For Simultaneous Delivery Of RNAi Agents	11/072592 (US), PCT/US2005/0017447, 2005/087926 (WO), 2005222084 (AU), 2558771 (CA), 0580013979.5 (CN), 05727680.0 (EP), 177862 (IL), 2007-502094 (JP), 20067020986 (KR), 550284 (NZ)
Therapeutic RNAi Agents For Treating Restenosis	11/251,076 (US), US05/037210 (WO)
Therapeutic RNAi Agents For Treating Psoriasis	11/256666 (US), US05/038139 (WO)
RNAi Agents For Maintenance Of Stem Cells	11/325244 (US), US06/000091 (WO)
Method For Detection And Characterization Of Short Nucleic Acids	11/340830 (US)
RNAi Expression Constructs	11/347028 (US), US06/004003 (WO)
RNAi Expression Constructs With Liver-Specific Enhancer/Promoter	11/355516 (US)
Multiple RNAi Expression Cassettes For Simultaneous Delivery Of RNAi Agents Related To Heterozygotic Expression Patterns	11/413628 (US), US06/016507 (WO)
Expression Modulating Agents-Ii	60/554861 (US)
Differential Expression Of Short Hairpin RNA By Mutagenized Or Hybrid Rna Pol III Promoters	60/792008 (US)
Modulation Of Hair Growth	11/244314 (US)

Benitec's Competitive Advantage

There are a number of challenges facing RNAi therapeutics and most relate to delivery. Benitec's core competitive advantage relates to delivery of siRNA. This enabling technology has the potential to rectify the existing drug-delivery bottleneck in the RNAi sector.

RNAi can be introduced into a cell by either an 'expression system' or a 'delivery system'. All the RNAi's in development using the Tuschl I and II patents, as well as the Crook 6,107,094 & 5,898,221 patents (094 & 221), need to be administered with a 'delivery system'. Benitec's technology delivers siRNA using an 'expression system'.

The 'expression system' uses a DNA construct inserted into a cell to trigger the expression of ddRNAi, which is cleaved into siRNA. The siRNA is the active agent against the dysfunctional gene causing the disease and targeted by the siRNA.

- Delivering siRNAi via synthetic RNAis into animals and humans is proving problematic. Most therapeutics in development requires direct administration to the site of concern, with systemic administration not practical using the current technology. For example, therapeutics in development are administered directly into tumours to treat cancer, directly into the eye to treat Age Related Macular Degeneration or directly into the lungs to treat Respiratory Syncytial Virus Infection.
- There are no seminal patents on delivering synthetic siRNA; resulting in various companies developing their own delivery technologies.

As an enabling technology, Benitec's expression patents have attracted a very high level of interest in the sector. It has the ability to circumvent many of the current issues on delivering synthetic RNAi and has the potential to accelerate development of clinically viable therapeutics.

Further Limitations of the RNAi and siRNA technology

As an emerging technology, there are further issues with RNAi and siRNA therapeutics that need to be resolved. It is likely that the response or severity of these issues will be different between synthetic RNAi and expressed RNAi. Only further research would elucidate how each platform technology would mitigate against various risks. Nevertheless, for the industry to find answers to these risks, each of the technologies will have to be assessed. This means that Benitec's expression platform is likely to be researched by various companies to determine the system that allows optimal performance of their RNAi therapeutic.

This also means that Benitec could extract further research licensing agreement similar to the Pfizer and Merck research evaluation agreement.

- It has been noted that siRNAs exhibits different effectiveness in different cell types. The reason remains elusive. Therefore, developers of RNAi therapeutics need to undertake significant research on the site of

delivery as well as the mechanism of delivery before a commercially viable therapeutic is developed.

- Partial specificity (or off-targeting) is an issue for many siRNA compounds. This is caused when the siRNA silences expression of a normal gene that has partial complementarity to the targeted gene. Although this risk can be mitigated by constructing RNAi to be homologous to the targeted gene⁷, isoforms of the targeted gene or similar members of the same targeted gene family could be affected.
- Over expression or over delivery of a siRNA or RNAi could induce an immune response against the siRNA, as well as other idiopathic immune problems.

Benitec's License Agreements

In October 2005, Benitec licensed Sigma-Aldrich research use of the technology in a US\$4.5m equity and licensing fee deal. Through Sigma-Aldrich, Pfizer took a non-exclusive research only license for the technology in February 2007. Benitec has signed various research only contracts with other companies. In 2004, Merck accessed a non-exclusive license for the technology. Other research use licenses were given to Chemicon, genOway, Artemis Pharmaceutical, IDT, GenScript, Ambion (Applied Biosystems) and Origen Technologies.

The company also has strategic cross licensing agreements with Alnylam and CombiMatrix, giving Benitec freedom to operate.

These agreements are not expected to provide significant revenue for Benitec. However, such agreements have two strategic purposes.

- It increases familiarity of the technology with sub-licensees and researchers who use the research kits supplied by the research kit licensees. Benitec's aim is for expressed ddRNAi to be the standard RNAi development synthesis method and become the method of choice within the industry.
- It increases use of the technology in the market and over time various groups will expand their research endeavours into clinical development programmes. At which point, these groups or companies will need a new license from Benitec.

Clinical Developments

The company is currently undertaking clinical trials on healthy HIV patients, through the City of Hope (Los Angeles). The company is also positively exposed to the Hepatitis C Virus Programme, licensed to Tacere Therapeutics in September 2006.

The HIV Trial

On 13 June 2007, the HIV trial commenced treatment of its first of five patients with HIV-associated Lymphoma. Estimated to be completed around June 2008, the trial is designed to assess the safety and feasibility of an Autologous Modified Stem Cell therapy.

If this pilot study is successful, an IND submission to undertake a Phase I study is anticipated to occur in late 2007 and the Phase I commence in the first quarter of the 2008 calendar year.

In monkey studies, the therapy achieved over 80% protection of T-Cells from HIV.

The study is funded with a US\$7.5m NIH grant, which should cover development costs to the end of Phase I.

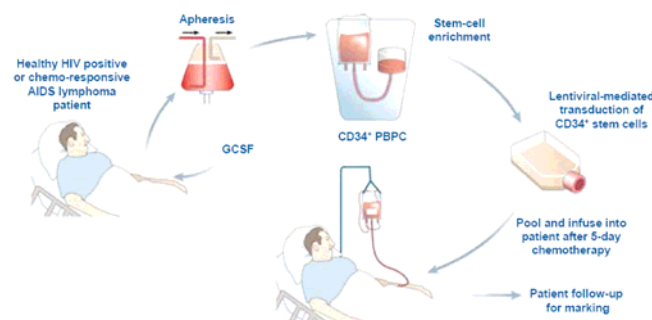
The Science behind the HIV Trial

This Phase I study is an RNA-based anti-HIV therapy where the expression vector used in Lentivirus and the cells used to host the expression system are hematopoietic progenitor cells (HPC). Lentiviruses can deliver a significant amount of genetic information into the DNA of the host cell, so they are one of the most efficient methods of a gene delivery vector.

The lentivirus vector encodes three anti-HIV sequences. These express RNAi as a;

- short hairpin RNA (shRNA) targeted to an exon in HIV-1 tat/rev,
- a decoy for the HIV TAT-reactive element,
- ribozyme that targets the host cell CCR5 chemokine receptor.

The HPC are enriched for CD34+ cells prior to transfection with the three-gene construct.



Diagrammatic representation of development of the City of Hope HIV Vaccine.
Source: Benitec

The HCV Trial

Tacere Therapeutics is a private company formed by the former executives of Benitec. The company is based in the US and currently seeking capital to undertake R&D and Clinical Trials.

The technology is based on RNAi elements targeting three separate, conserved regions of the Hepatitis C virus, thus hopefully preventing the generation of viral escape mutants.

Under the agreement, Benitec secured undisclosed upfront payments, a scale of milestone payments and a potential future royalty stream by licensing its gene silencing technology for treating Hepatitis C. Benitec also holds 5% equity in Tacere. Tacere still has to fully pay Benitec under the agreement.

The Trials are more about Testing the Science than Developing a Therapeutic

There is enormous competition in the HIV vaccine and therapy space, with 100's of various cellular- and immuno-therapies in development. However, all that have completed trials have failed.

We do not believe that Benitec's HIV cellular therapy trial will be a commercial success, simply because Benitec's targets are Tat and Rev, which are involved in the replication process. Replication inhibition is required to be near 100% for the duration of the therapy and be more effective and less expensive than HAART.

We do believe that Tacere's HCV therapy has a higher probability of being commercial successful, yet there is a high level of competitive HCV inhibitors in development. In addition HCV patients tend to be difficult to treat as they are mostly drug users and not compliant to therapeutic drug routines. Nevertheless, in our opinion the HCV programme has a higher chance of being a commercial success than the HIV programme, because current treatment is a combination of Pegasys® and ribavirin that is not overly effective and expensive. The HCV RNAi therapy is targeted to the NS5B region of the virus. RNA replication takes places via the viral RNA-dependent RNA polymerase of NS5B, which produces a negative-strand RNA intermediate. The negative strand RNA then produces new positive-strand viral genomes⁸, which suggests that NS5B inhibition could be an effective method of managing the disease. In addition, small molecules targeting NS5B have encountered resistance⁹, indicating a new strategy to target replication is required.

We see the real success of the trials as validation of the ddRNAi technology. Remembering that ddRNAi is an unproven therapeutic technology, any activity demonstrated against HIV, HCV or clinical markers to the disease caused by these viruses would be extremely positive. Any positive outcomes would markedly increase the value of the technology as it would be first time ddRNAi demonstrates clinical viability. Although a successful trial is unlikely to

produce a commercially viable HIV or HCV therapy, the interest in the technology would encourage others to explore its use for other indications. Third parties developing ddRNAi therapeutics would require a license from Benitec.

Financial Position

On 4 April 2007, the company raised \$5.3m via a rights issue through subscription of 53m shares at 10¢ per share. In addition, 56m options were issues carrying a strike price of 15¢ per share.

The company has cash that could see it progress for about one year, but this is conditional upon the outcome of the current legal dispute and the cost of defending and/or enforcing '099'.

Share Structure @ 24 July 2007

Ordinary Shares			
286,649,618			
Options and Warrants (expiration date)			
56,081,915	\$0.15 (3 Apr 11)	6,126,962	\$0.90 (4 Aug 14)
41,433,069	\$0.32 (6 Apr 08)	1,953,125	\$0.17 (23 Oct 15)
250,000	\$0.07 (20 Nov 11)	3,000,000	\$0.025 (4 Sep 11)
100,00	\$1.00 (28 Jul 09)	1,000,000	\$0.025 (14 Sep 11)
100,00	\$0.50 (28 Jul 09)	1,000,000	\$0.067 (14 Dec 11)
150,000	\$1.50 (28 Jul 09)	17,560	\$0.03 (30 Sep 13)
150,000	\$2.00 (28 Jul 09)		

Recommendation

Benitec is a high risk investment opportunity for investors knowledgeable and tolerant of the investment risks associated with investing into an early stage biotechnology company.

The company's key assets are its patents, which are the seminal patents covering cellular RNAi expression. And as these patents control ownership over RNAi expression, Nucleonics has constantly and persistently challenged the validity of these patents.

Therefore, the value in Benitec is wholly and totally reliant upon the outcome of the USPTO's re-examination of the pivotal patent '099'.

- Success with the USPTO will mean that the any company seeking to develop an ddRNAi expression system for research or clinical use must acquired a license from Benitec prior to commercialisation of their product
- Failure with the USPTO will mean that Benitec's core value is extinguished.

⁸ http://en.wikipedia.org/wiki/Hepatitis_C_virus

⁹ Business briefing: North American Pharmacotherapy 2005

It is too early to place a valuation upon the company because of the early stage nature of the drug development programmes and uncertainty over the IP. Nevertheless based on comparable companies, we are confident that the likelihood of Benitec becoming acquired increases and the company should increase in value to become more representative of its international peers.

Company	Market Cap
Generex	US\$171m
Nastech	US\$322m
Senesco Tech.	US\$417m
Oxford BioMedica	£233m
Benitec	A\$40.3m

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Prepared by Darren J. Grubb PhD MBA GDipAppFin