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# ASX RELEASE

## Update on Progress with Therapeutic Programs

## Sydney, June 19, 2012

Gene silencing company Benitec Biopharma (ASX: BLT) today announced a detailed progress update (attached) of its multiple technology programs aimed at novel human therapeutics.

The update highlights progress towards human clinical studies for the company's key programs targeting a range of major unmet human medical needs. The update follows a meeting of the Company's Chief Investigators Group in May. Interviews with members of the Chief Investigators Group can be viewed at www.youtube.com/user/BenitecNews

Benitec Chief Executive Officer Dr Peter French said, "The update demonstrates the progress we are making by pursuing a risk-managed business model for our proprietary gene silencing platform technology.

"The depth of our gene silencing product pipeline aimed at developing multiple therapeutic products clearly demonstrates we are not dependent on the success of any one particular product. This reduces our execution risk and gives us multiple shots at success.

"The update also highlights our strong senior clinical partnerships and collaborations with leaders in the field of ddRNAi worldwide.

"Each therapy program has been carefully selected to rapidly build on the strong accumulated evidence to date and demonstrate the wide applicability of Benitec Biopharma's gene silencing technology as a transformational solution to unmet human disease."

***The attached update document provides information for investors including:***

*Cancer-associated Pain*

- Testing of lead compounds that are identified as conserved across all test species confirmed strong activity against the target gene and this conservation greatly simplifies pre-clinical testing
- A GMP manufacturer has commenced production of material suitable for pre-clinical and clinical trials
- Benitec Biopharma's CEO had an encouraging informal briefing meeting with the European Medicines Agency (EMA) in London on May 23rd giving a clearer understanding of the regulatory pathway

*Non-small cell lung cancer (NSLC)*

- Confirmation of nanoparticle/ddRNAi construct integrity
- Confirmation that a single i.v. injection of the delivery vehicle (Jet PEI) can reach the lung and enter tumour cells *in vivo*
- Preliminary evidence that there are no gross immunological or obvious adverse metabolic effects from injecting the construct *in vivo*
- This data is very encouraging, and increased numbers of animal tests are underway to confirm the early data
- The next step is to conduct extensive biodistribution studies

*Hepatitis B (HBV)*

- Dr York Zhu from Biomics reported that the program is on track to deliver its expected outcomes
- Construct optimisation *in vitro* is close to finalisation – top three sequences selected and promoter modifications (to ensure lack of toxicity) completed
- Incorporated advice from Dr David Suhy from Tacere Therapeutics
- Construct target sequences are conserved across all genotypes worldwide, making the final product likely to be broadly applicable
- *In vivo* validation in mouse model will commence shortly

*Oculopharyngeal Muscular Dystrophy (OPMD)*

- Professor George Dickson from Royal Holloway, University of London, reported excellent progress in the six months since the program commenced
- single ddRNAi constructs produce around 65% gene knock down *in vitro*
- ddRNAi constructs expressing multiple shRNA sequences have been made and are being tested
- preliminary *in vivo* studies demonstrate encouraging levels of normal target gene expression in muscles from viral-delivered gene constructs

*HIV/AIDS*

- Professor John Rossi from the City of Hope HIV/AIDS trial reported that the ddRNAi construct still expresses 3.5 years after the patients' stem cells were transfected with a lentivirus construct
- Benitec Biopharma's licensee Calimmune is aiming to commence a clinical trial in HIV/AIDS patients commencing in 2012. This trial will be the first to use only ddRNAi constructs to target HIV in patients

*Hepatitis C*

- Dr David Suhy from Benitec Biopharma's US-based licensee Tacere Therapeutics reported that the program has progressed to the point where an IND submission is in preparation, and a substantial portion of clinical trial material has been manufactured
- Advanced discussions have been held with the FDA
- A US-based clinical trial of TT-034 is possibly ready to start as soon as early 2013. This would have a significant potential benefit for Benitec Biopharma as a further clinical demonstration of the safety and efficacy of ddRNAi-based therapies

***Revised Gantt charts are presented below. The key points are:***

- The modified pain clinical development timeline is based on discussions with regulators, regulatory consultants, and our GMP manufacturer. The timeline has increased beyond initial estimates due to this advice and some key operational constraints and strategic decisions
- The lung cancer program is running behind the previous estimates due to the longer than expected time taken to optimise the ddRNAi construct/Jet-PEI mixture and its use in the *in vivo* lung cancer model at the CCIA
- The hepatitis B program is on track

| Pain, Hepatitis B and Non-small Cell Lung Cancer Programs | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Milestones** | | 2012 | | 2013 | | | | 2014 | | | | |
| | | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | |
| Proof of concept / *in vivo* validation | Pain | | | | | | | | | | | |
| | NSCLC | | | | | | | | | | | |
| | HBV | | | | | | | | | | | |
| Manufacturing/Production | Pain | | | | | | | | | | | |
| | NSCLC | | | | | | | | | | | |
| | HBV | | | | | | | | | | | |
| Toxicology and biodistribution studies | Pain | | | | | | | | | | | |
| | NSCLC | | | | | | | | | | | |
| | HBV | | | | | | | | | | | |
| Clinical trial approval | Pain | | | | | | | | | | | |
| | NSCLC | | | | | | | | | | | |
| | HBV | | | | | | | | | | | |
| Clinical trial | Pain | | | | | | | | | | | |
| | NSCLC | | | | | | | | | | | |
| | HBV | | | | | | | | | | | |

**For Further Information**

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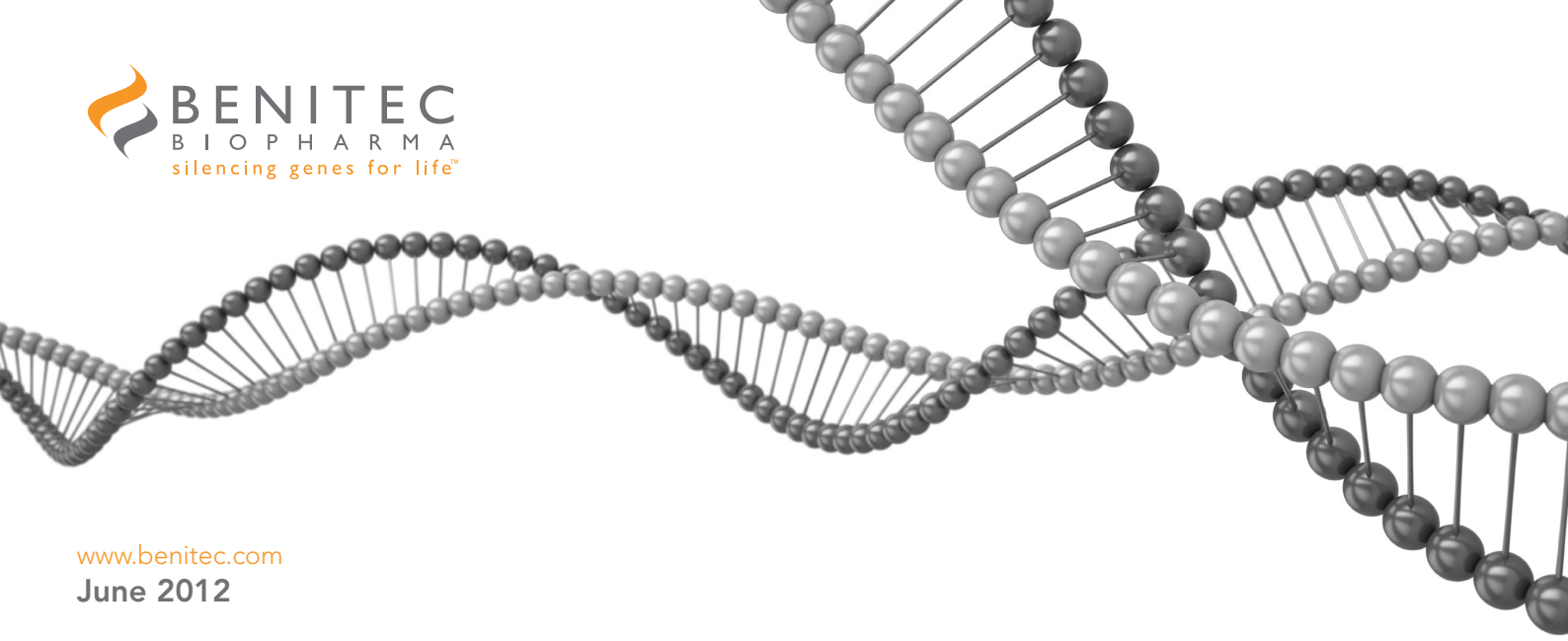
**About Benitec Biopharma**

Benitec Biopharma Ltd is developing novel treatments for chronic and life-threatening conditions based on targeted gene silencing activity using a transformational technology: DNA-directed RNA interference (ddRNAi) - sometimes called expressed RNAi. The technology's potential to address unmet medical needs and to cure disease results from its demonstrated ability to permanently silence genes which cause the condition. Importantly, this technology's target gene and related gene pathways will rarely have presented as a therapeutic avenue for research for the traditional small molecule agents, currently accounting for the majority of today's pharmaceutical products.

Founded in 1997 and trading publicly since 2001, Benitec Biopharma is listed on the Australian Securities Exchange (ASX) under the symbol "BLT". Benitec Biopharma aims to deliver a range of novel ddRNAi-based therapeutics to the clinic in partnership with the pharmaceutical industry. Besides a focused R&D strategy in infectious diseases, cancer and chronic cancer-associated pain, Benitec Biopharma is pursuing programs with licensees that have advanced to pre-clinical and/or clinical trials.

Benitec Biopharma videos can be viewed at www.youtube.com/user/BenitecNews

BENITEC BIOPHARMA
silencing genes for life™



www.benitec.com
June 2012

## Contents



# Transformative gene silencing technology for unmet medical needs

## A short history of RNAi and basic mechanism

In 2006, US scientists Andrew Fire and Craig Mello won the Nobel Prize in medicine for their work on RNA interference (RNAi). The tiny RNAi molecules upended biological dogma by unveiling a brand new kind of genetic messenger that can block the function of other genes like an off switch. The technology provides new avenues for discovering and developing new medicines.

RNAi involves introducing double stranded (ds)RNA into a cell, one strand of which is identical to part of the sequence of the messenger RNA of the gene being targeted to be silenced or knocked down. The cell identifies the dsRNA as an intruder (because the cell usually only produces single stranded RNA) and destroys it.

In the process, the target RNA is also destroyed, thereby switching off the function of that gene. Benitec's unique version of RNAi, DNA directed or ddRNAi, involves inserting a DNA construct into a cell, triggering the production of dsRNA in the form of a short hairpin RNA (shRNA), which is then converted into small interfering RNA (siRNA) as part of the RNAi process. This destroys the target mRNA and silences the expression of the target gene.

RNAi has an important role in defending cells against parasitic infections like viruses and controlling gene expression in general. Manipulating this endogenous process has many medical applications.

## Competitive advantage of ddRNAi over siRNA

At the same time that Fire and Mello were conducting their research, scientists from the Commonwealth Scientific and Industrial Research Organisation (CSIRO), in particular Benitec Biopharma's Chief Scientist Dr Michael Graham, were working in a similar field. The work gave rise to Benitec's ddRNAi technology which is exclusively licensed from CSIRO. ddRNAi differs significantly from synthetic siRNA, and offers a number of technical advantages, principally longevity of the effect and continued production inside the cell of the dsRNA. The gene silencing effects of laboratory-produced siRNAs are transient, therefore they must be continuously administered like any conventional drug. ddRNAi therapies offer the possibility of permanent silencing of genes leading to long lasting treatments and potential cures for many conditions.

This is achieved by delivering DNA coding for specific sequences of dsRNA into target cells. After processing by cellular enzymes the resultant single stranded RNA pairs with the target messenger RNA and 'silences' its expression. The result is that the specific protein associated with the disease is not made and the course of the target disease can be altered, or even stopped. Once delivered, the DNA construct continually expresses the dsRNA, hence there is no need to continually administer synthetic RNA, as gene silencing can be maintained indefinitely.

Delivery of RNAi-based therapeutics to affected tissues is a significant challenge, particularly for siRNA therapeutics. A common approach is to introduce synthetic siRNA molecules into a cell by incorporating them into various types of nanoparticles, but delivery of siRNA remains a major hurdle. ddRNAi overcomes this as it is able to be delivered using well-characterised gene therapy vectors (benign viruses being the most common option, but non-viral approaches are also used) which can deliver DNA into cells with high efficiency. Such vectors have been widely trialed in humans and have been shown to be safe and effective.

Benitec Biopharma's transformative ddRNAi technology has the potential to address many common unmet medical needs. The company is currently building proof-of-concept data in four major disease programs – cancer pain, hepatitis B, lung cancer and muscular dystrophy. Benitec Biopharma is collaborating with leading international experts to develop gene silencing therapies for these four chronic life-threatening diseases and disorders for which there are no lasting current medical treatments.

In addition, Benitec Biopharma has sub-licensed its ddRNAi technology for other infectious disease therapeutic programs in Hepatitis C (to Tacere Therapeutics Inc, USA) and HIV/AIDS (to Calimmune, USA).

This brochure aims to give you a brief description of, and a status update for, each program involving our exciting ddRNAi gene silencing technology.

## The global RNA market potential

By 2017, the global market for RNA interference technology is estimated to be worth US$4 billion annually. The US and Europe represent the largest markets, with Europe expected to grow rapidly. The longer-term RNAi market will be driven by the positive results from the R&D of RNAi therapeutic drugs for various diseases. With many blockbuster drugs expected to lose their patents in the next few years, it is likely large global pharmaceutical companies will seek to increase their investment in new RNAi therapies that will help maximise their chances of launching novel new drugs.

## Benitec's secure RNAi intellectual property position

Benitec Biopharma has a leading global position in gene silencing using ddRNAi. Benitec holds a non-revocable, exclusive worldwide license from CSIRO for the development and commercialization of all human therapeutic applications under the '099 Graham Patent, and an exclusive worldwide license to CSIRO's Waterhouse family of patents. The company is focused on leveraging its strong intellectual property position to out-license and partner its technology along the entire drug development process.

The '099 Graham Patent has been the subject of a number of challenges and in 2011 was successfully re-examined and reissued to Benitec in the US and allowed in the EU, adding to those already granted in other key jurisdictions including Australia, Japan, South Africa, India, China, Canada and the UK. Benitec's patent estate contains key claims covering methods for silencing genes by generating dsRNA inside a cell from a genetic construct.

In addition to the CSIRO-licensed patents, Benitec Biopharma holds several other granted patents for specific applications and improvements of the ddRNAi technology. Benitec currently has over 100 patents and patent applications and has in-licensed several additional patents that extend the scope of its patent estate and enhance the utility and value of its RNAi platform.

## About Benitec Biopharma's Chief Investigator's Group

Benitec Biopharma's pipeline of new therapeutics is being developed in close collaboration with leading global experts in the field. In 2011, Benitec established a Chief Investigators' Group (CIG) to bring together its scientific founders with its leading collaborative partners worldwide. The CIG reflects the company's collaborative approach and the clinical focus of its commercial programs. The members of the CIG are all acknowledged international experts in the field of RNAi therapeutics. The group meets regularly and is chaired by CEO Dr Peter French. All members are appointed on a voluntary basis. The profiles of the CIG Members are below:

## Chief Investigator's Group profiles

**Dr Michael Graham** PhD
Benitec Biopharma's Chief Scientist

Dr Graham's research interests are in the field of molecular genetics, with a particular focus on the applications of RNAi in biotechnology. He commenced the development of Benitec's ddRNAi technology while working in plant biotechnology at CSIRO and continued this work at QDPI and Benitec, focusing on medical applications; the core Benitec patent portfolio was developed at this time. Dr Graham spent five years at the University of Queensland working with RNAi in plant biotechnology in an industry collaborative program. He has published over 35 scientific papers and many patents. In January 2012 Dr Graham re-joined Benitec Biopharma as Chief Scientist.

**Dr Ken Reed** BSc MSc PhD FATSE

Dr Reed was the scientific founder of Benitec. Dr Reed was the founding director of QABC and previously a co-founder of Advanced Breeding Technology Pty Ltd, the first company to commercialise the use of PCR. He was Deputy Chair of the inaugural Australian Biotechnology Advisory Council and served for many years on the Australian Government's Genetic Manipulation Advisory Committee and the Board of the Australian Genome Research Facility. Dr Reed is a Fellow of the Academy of Technological Sciences and Engineering.

**Dr John J Rossi** PhD

Dr. Rossi is the Lidow family Professor and Chair of the Division of Molecular Biology, Beckman Research Institute of the City of Hope, and Dean, Graduate School of Biological Sciences, Beckman Research Institute of the City of Hope, Duarte, California. Dr. Rossi received his doctoral training in genetics at the University of Connecticut in Storrs and postdoctoral training in molecular genetics at Brown University. His research has focused on RNA biology and clinical applications of small RNAs. He is the recipient of an NIH Merit award for his work on ribozymes and HIV. Work in the laboratory continues to focus upon

mechanisms of small RNA mediated inhibition of gene expression and RNA based therapeutics, with recent emphasis on function and applications of RNA interference and expressed short hairpin RNAs for therapeutic treatment of HIV and cancers. He has published over 200 peer reviewed articles and numerous reviews and commentaries on RNAi based therapeutics.

**Hear Dr Rossi speak about Benitec and ddRNAi here: http://www.youtube.com/watch?v=DzmJYSmaBuc**

**Dr York Zhu** PhD

Dr. York Zhu, the founder of both Biomics and NT Omics Inc., has 20 years R&D and business experience. He started his industrial R&D career at Clontech Labs (1993) as an R&D Manager following several years as an academic in Memorial Foundation in Nagoya, Japan (1987-1989). In 2000, Dr. Zhu worked as Chief Technology Officer in Genemed R&D headquarters for 4 years, where he was an inventor on several patents and led the R&D team to develop a gene drug discovery technology platform. Then as Vice President and Chief Scientist of Zytogene (a spin-off of Genemed) he managed R&D operations to successfully develop over 200 new products for Zymed, which brought the company to a high market value and was acquired by Invitrogen. In 2005, Dr, Zhu founded NT Omics, and invented Entire siRNA targets (EsT) library technology which filled the gap in this field. In 2006 Dr. Zhu established Biomics in Nantong, China, where he now serves as CEO and Chairman. The Company is a leading player in RNAi in China.

Dr. Zhu undertook his PhD at the Medical School of Nagoya University (Japan,1989-1993), and his MS in Nantong University (1982-1985). During his career, Dr. Zhu has published more than 30 papers, held 3 patents and has 6 more applications.

**Hear Dr Zhu speak about Benitec and ddRNAi here: http://www.youtube.com/watch?v=_tiTtEVixCA**

**Professor Maria Kavallaris** BAppSci UTS, PhD UNSW

Professor Maria Kavallaris is Head of the Tumour Biology and Targeting Program at the Children's Cancer Institute Australia, Lowy Cancer Research Centre, and holds a conjoint academic appointment in the Faculty of Medicine, University of New South Wales (UNSW), Sydney, Australia. She is a National Health and Medical Research Council (NHMRC) Senior Research Fellow and Director of the Australian Centre for Nanomedicine, UNSW. Professor Kavallaris's research contributions include identifying the mechanisms of action and resistance to anticancer drugs that target cell division; discovering new cytoskeleton interactions in cancer; and the development of less toxic cancer therapies using nanotechnology.

Her research contributions have been recognised by a number of awards and prizes including a NHMRC Career Development Award, a Young Tall Poppy Award, and an Australian Museum Eureka Prize. Professor Kavallaris has authored over 85 publications, edited a book on the cytoskeleton and human disease and authored a number of book chapters. Professor Kavallaris serves on the Board of the Australian Institute for Policy and Science and has served as President of the Australian Society for Medical Research.

**Professor George Dickson**

Professor Dickson is Chair of Molecular Cell Biology at the Royal Holloway, University of London, UK.

He is working on programs in the field of the molecular genetics and gene therapy of neuromuscular, cardiovascular and neurodegenerative diseases. His research program involves development of gene therapeutics (lentiviral, adenoviral, adeno-associated virus, non-viral lipoplex vectors, oligonucleotide-based pharmaceuticals), use of transgenic animals and the understanding of signaling pathways in relation to the pathophysiology and treatment of the muscular dystrophies, atherosclerosis and hyperlipidaemia, and neurodegenerative disease. The work is supported by the European Union, UK Medical Research Council, UK Department of Health, Wellcome Trust, Muscular Dystrophy Campaign, Action Duchenne, Gates Foundation, and the Association Français Contre les Myopathies.

**Hear Professor Dickson speak about Benitec and ddRNAi here: http://www.youtube.com/watch?v=IT5kWXGdJog**

**Dr Geoff Symonds** PhD

Dr Symonds is Chief Scientific Officer of Calimmune Inc and has a Conjoint Professor appointment at the University of New South Wales.

He is working on cell-delivered gene therapy for HIV/AIDS. The approach involves modifying hematopoietic stem cells and CD4+ T lymphocytes with anti-HIV genes and then re-introducing these cells to the individual to impact on CD4+ T cell count and HIV viral load. The anti-HIV genes are introduced with a self-inactivating lentiviral vector. Dr Symonds has an extensive background in this area as well as research on the molecular basis for solid tumours and leukaemia. His HIV gene therapy clinical development work in Australia is supported by Calimmune, and grants from the Australian Research Council and Research Infrastructure Support Services.

**Dr David Suhy** BSc, PhD

Dr Suhy is the Director of Research and Development at Tacere Therapeutics. He is one of the inventors of TT-033. He has directed the development of the TT-03x series of compounds designed to treat patients infected with the Hepatitis C virus from design to IND-enabling studies and will continue to lead the program as it is poised to enter the clinic in early 2013. His involvement in the program started as a senior scientist at Avocel, an RNAi therapeutics company, in 2003, and continued after the company was acquired by Benitec Ltd. in 2004. David's other scientific roles include: Associate Director of R&D at Clontech; Principal Scientist at Antara Biosciences, and leading the Target Validation Group at PPD Discovery. He earned his PhD in Biochemistry, Molecular Biology and Cell Biology at Northwestern University, and conducted his post-doctoral work at Stanford University.

**Hear Dr Suhy speak about Benitec and ddRNAi here: http://www.youtube.com/watch?v=791fPHsD_1M**

# Cancer-associated neuropathic pain

## The market

The global market for cancer-associated pain treatments is estimated at US$2 billion per year. This is expected to increase to over US$2.9 billion by 2016. Neuropathic pain is a common and very difficult to treat condition in cancer and frequently results from compression on the central nervous system by a tumour or as a side effect of chemotherapy, radiation or surgery. Opioids are the main therapeutic option although they frequently give rise to severe side-effects and patients frequently become resistant to their anaesthetic effects.

## Benitec's program and current status

We believe this program holds the greatest near term commercialisation and licensing opportunities of our current in-house programs. Our pre-clinical work is focused on developing and testing a ddRNAi construct (*Nervana*™) to silence a gene (PKCγ) expressing a key molecule in the spinal cord which has been clearly demonstrated to be responsible for mediating neuropathic pain in the central nervous system. Using a lentiviral vector, the construct is delivered to the target nerve cells, where it integrates and continuously expresses an shRNA silencing molecule for the target gene, reducing the expression of the pain mediator to low levels so that effective and long lasting pain relief might be achieved.

Ideally, a single spinal cord injection will be sufficient to provide this long lasting pain relief. *In vivo* proof of concept of this approach has been recently demonstrated pre-clinically by another group, giving independent confirmation of the efficacy of the approach.

At the May 2012 CIG meeting, Dr Graham provided the following update to the Board on the status of the pain program: "Following the decision in 2011 to focus on the protein kinase C gamma (PKCγ) gene, design and testing of specific functional gene silencing constructs began. These constructs were designed, manufactured and their activity confirmed *in vitro*. Pre-clinical *in vivo* studies verifying the safety and efficacy of Benitec's lead compounds are in progress. Together with researchers at TetraQ at the University of Queensland and a recently appointed research group in the US, we plan to complete efficacy and preliminary safety studies in 2012. Our plan is to then conduct toxicology studies which will support approval for a clinical trial involving terminally ill cancer patients suffering severe neuropathic pain. Given that the target is well validated, we have pursued a research strategy that will streamline the pre-clinical testing of this novel therapeutic. To this end we have designed and successfully tested *in vitro* new ddRNAi constructs that target sequences on the PKCγ gene that are absolutely conserved between humans and the likely pre-clinical test species. This allows the testing of a single therapeutic entity through all phases of the pre-clinical program, regardless of test species. Planning of pre-clinical pharmacology and toxicology testing is well advanced.

Eight constructs were tested in cell lines transformed with lentiviral vectors; three constructs (3, 4 & 5) markedly silenced PKCγ mRNA, two of these are currently being tested in rat pain models (Figure 1).

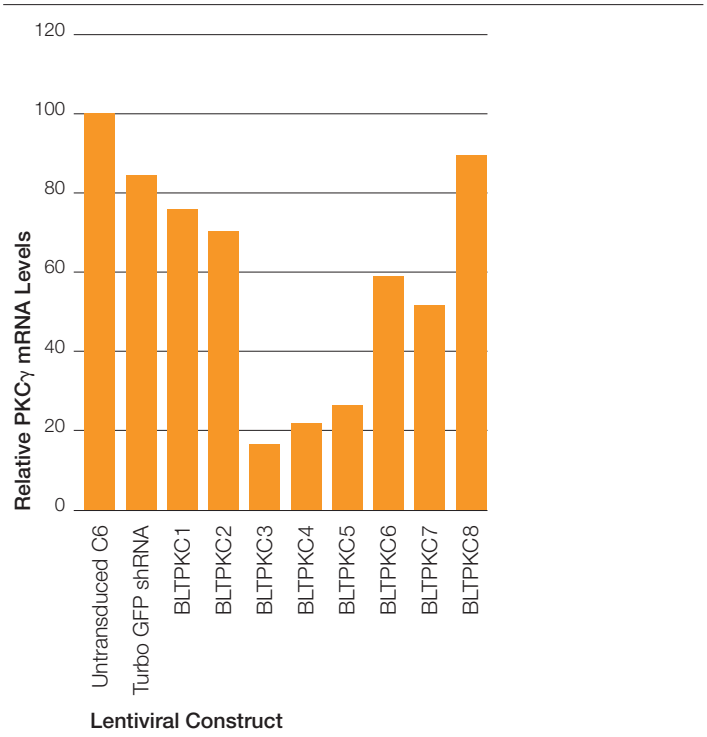



**Figure 1.** Efficacy of silencing of PKCγ *in vitro* by various ddRNAi constructs

Another critical aspect of this work is to partner with a group who can provide high quality lentiviral particles, ultimately under Good Manufacturing Practices (GMP) standards. We have identified a group with such abilities. Importantly this group can also provide Benitec with Freedom to Operate using such vectors. We are very confident of optimising the lead gene sequence in 2012 and incorporating this into a pre-investigational new drug submission."

## Preliminary European Medicines Agency (EMA) discussions.

On his recent visit to the UK, Benitec Biopharma's CEO, Dr Peter French, arranged to have an informal briefing meeting with some members of the EMA to discuss Benitec Biopharma's cancer-associated pain program. Some very positive feedback and constructive suggestions were made, indicating significant interest in Benitec Biopharma's novel approach to pain. On the basis of these discussions and in consultation with a European regulatory consultant, the timings for the pain program to enter the clinic have been adjusted to reflect the regulatory requirements in both Europe and the US.

## Benitec Biopharma's Pain Program to be presented at the 6th Pain Summit in San Francisco in October.

World experts in the pain management and therapeutics field are meeting in San Francisco, CA on October 3 and 4 to discuss recent drug discoveries, preclinical developmental trends and newly marketed products. Dr. Peter French, CEO of Benitec Biopharma, has been invited to present Benitec Biopharma's novel strategy in pain control using gene therapy (Figure 2). This approach offers the prospect of a single treatment providing long term pain relief by using intrathecal delivery of lentiviral particles expressing shRNA constructs designed to inactivate the Protein Kinase C gamma gene in neurons of the spinal cord. This will result in significant exposure of the Benitec Biopharma program to pain experts, pharmaceutical companies and clinicians who will have the ability to assist Benitec Biopharma in the clinical and commercial development of this program.

## Project Timelines

The modified *Nervarna*™ clinical development timeline below has been based on discussions with regulators, regulatory consultants, and our lentiviral GMP manufacturer. The timeline has increased beyond initial estimates due to this advice and some key operational constraints and strategic decisions, including the decision to change the target to PKCgamma, the decision to design new constructs that are conserved between test species, the decision to contract a lentiviral GMP manufacturer at an earlier stage than anticipated, and the time for manufacture of the customised lentiviral constructs. Having achieved most of these goals to date, the delivery of the manufactured constructs will trigger the milestones listed below. Additionally, discussions with the EMA and regulatory consultants has led us to modify the original estimated time to achieve clinical trial approval. Nevertheless this remains a rapid clinical development path for a genetic therapy.

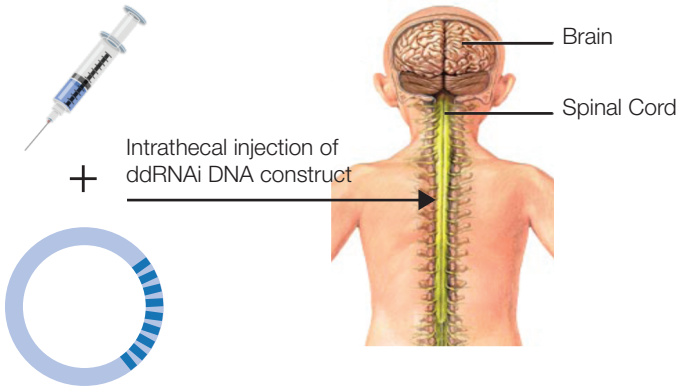



**Figure 2.** Benitec's strategy for pain relief in cancer patients. A ddRNAi construct in a lentiviral vector (circle) is injected into the spinal chord of patients. Such intrathecal injections are a commonly used medical procedure. The vectored ddRNAi construct will integrate into the chromosomes of neuronal cells and express an shRNA that will permanently silence the PKCγ gene hence providing long-term pain relief.

| *Nervarna*™ | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Milstones** | **2012** | | **2013** | | | | **2014** | | | |
| | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| *In vivo* validation | ▶ | | | | | | | | | |
| Pre-pre-IND / Scientific advice EMA | | ▶ | | | | | | | | |
| Lentiviral manufacturing | ▶ | | | | | | | | | |
| Toxicology & biodistribution studies | | ▶ | | | | | | | | |
| | | | | | | | | | | |
| Clinical trial approval | | | | ▶ | | | | | | |
| Phase I trials | | | | | | ▶ | | | | |

# Drug Resistant Lung Cancer

## The market

Lung cancer is the most common cause of cancer death in the Western world with non-small cell lung cancer (NSCLC) accounting for the majority of lung cancer types. Only about 15 per cent of patients will survive more than five years from time of diagnosis. The use of chemotherapy to treat NSCLC is limited by its toxic effects and the emergence of treatment-resistant cancers. There is a large unmet medical need for treatments that can be used at lower doses, or which can avoid resistance.

## Benitec's program and current status

Benitec Biopharma is working with the Children's Cancer Institute Australia (CCIA) at the University of New South Wales (UNSW) to develop a ddRNAi-based therapy to overcome chemotherapy resistance in human NSCLC cells. The target gene for silencing is called betaIII (βIII)-tubulin.

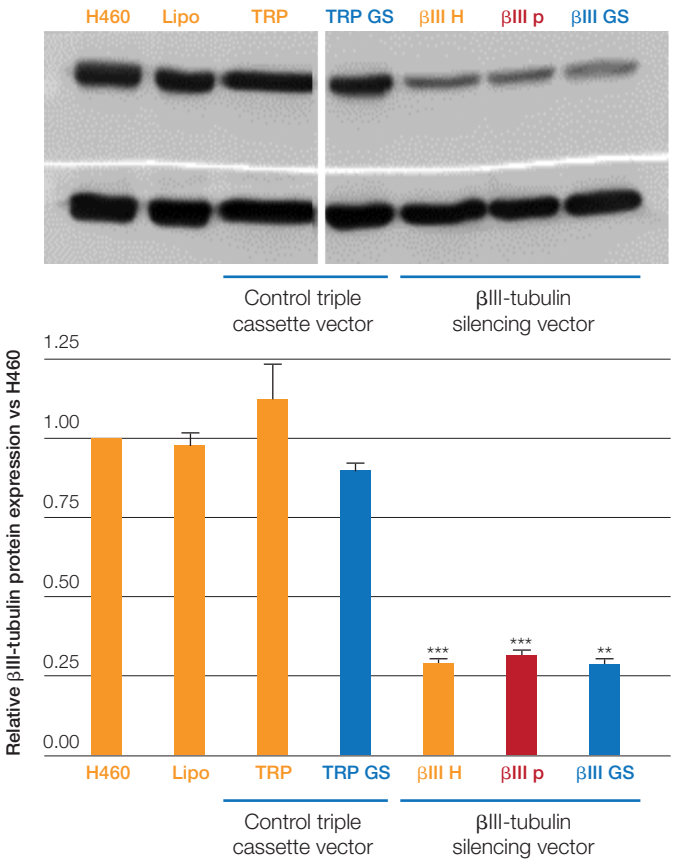



**Figure 3.** Reduction of beta III tubulin protein by Benitec Biopharma's ddRNAi construct in human lung cancer cells *in vitro*. H460 = Non transfected lung cells; Lipo = Lipofectamine only, TRP = Control triple cassette vector; TRP GS = Control triple cassette vector; H, P and gs are different βIII Triple cassette vectors.

The program stems from research work by Professor Kavallaris and her fellow researchers in which they aimed to understand the role of βIII-tubulin in cancer cells. βIII-tubulin is not expressed in most normal cells, but it is switched on in a high proportion of NSCLCs where it causes cancer cells to become resistant to chemotherapy. The group used ddRNAi constructs to switch off βIII-tubulin in the cancer cells and showed that these cells were now sensitive to chemotherapy. These laboratory results tell us that this is a promising means for making chemotherapy drugs more effective against lung cancer, and that ddRNAi can potentially be used as a co-therapy with conventional chemotherapy. Since Benitec Biopharma sponsored the program, "super silencing constructs" that contain three silencing sequences have been designed and demonstrated to make this effect even more pronounced *in vitro* (Figure 3). This provides evidence that Benitec's approach of delivering a gene silencing molecule has real potential in the clinical setting for lung cancer.

The aim is to substantially increase the efficacy of current chemotherapy for lung cancer patients resulting in lower toxicity-related effects, improved quality of life and potential extension of life.

At the May 2012 CIG meeting, CCIA Project Leader researcher Dr Josh McCarroll provided the following update to the Board on the status of the program:

"Our lung cancer program has met all of its early milestones and pleasingly has demonstrated the potential to almost completely silence βIII tubulin that is associated with chemotherapy drug resistance in human lung cancer cells. Extensive work over the last six months has gone into developing a powerful animal model of human lung cancer. We implant human NSCLC cells into mice, where we can get reproducible growth of tumors and we can actually image the growth of these tumors in living animals, this is a significant research tool developed at the CCIA.

"A key milestone of the program that we are aiming to achieve in 2012 is to demonstrate the ability to deliver the construct to human lung cancer cells *in vivo* using mice as a model. The first of those experiments was concluded in late 2011, with very encouraging results. From an intravenous injection, the construct was delivered to the lung cancer with no apparent adverse effects, and with silencing of the target gene. Whilst a preliminary result, this was a highly significant step, as it provides evidence that delivering the gene silencing molecule systemically has real potential in the clinical setting for lung cancer.

In 2012 we have been working on optimising the model and conducting further *in vivo* studies in larger groups of animals to confirm that this approach to βIII silencing is effective as well as having no obvious adverse effects. This work is still in progress, but if these results confirm the initial finding, given everything we know about our preclinical data in terms of the role of this protein in chemosensitivity, we are confident we'll see an enhanced effect in terms of the treatment of lung cancer with chemotherapy both preclinically and clinically."

In a subsequent update, Professor Maria Kavallafis reported that very recent data shows that both short and long term intravenous adminstration of the ddRNAi constructs complexed with the proprietary delivery vehicle Jet-PEI™ appears to cause no adverse immune or gross morphological effects, and that the delivery vehicle is capable of delivering the ddRNAi constructs to the lung tumour cells growing in mice (Figure 4). With two research scientists dedicated to the project, Benitec Biopharma expects that substantial data will be generated from the orthotopic *in vivo* model, which is a close simulation of the clinical situation. This will provide Benitec Biopharma with impressive evidence for regulators when developing clinical trial documentation.

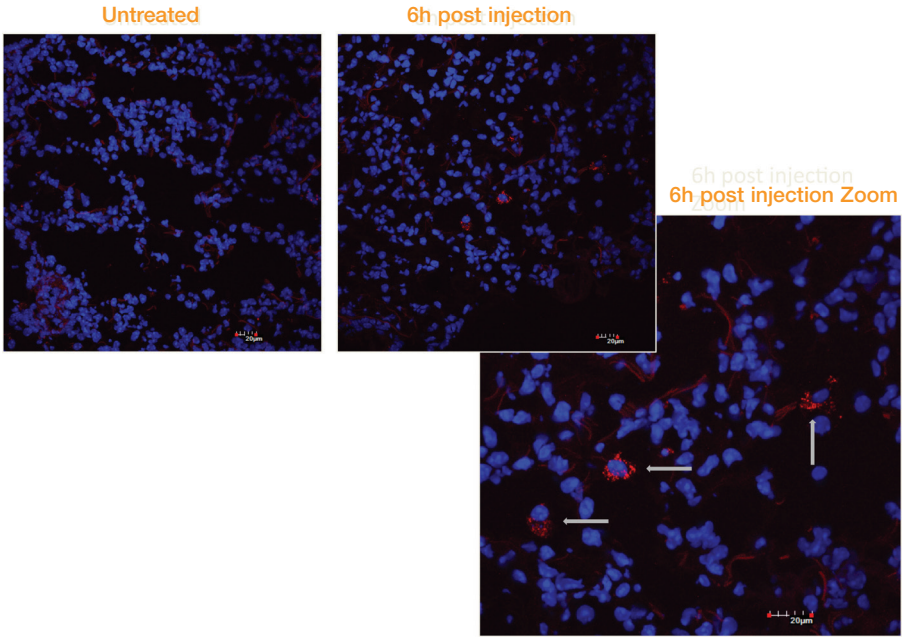



**Figure 4.** Human lung cancer tumours take up Jet PEI™ from a single intravenous injection. The red dots (arrows) inside the cells show the Jet PEI particles.

## Timelines

This program is running behind the previous estimates due to the time taken to optimise the ddRNAi construct/Jet-PEI mixture and its use in the *in vivo* orthotopic lung cancer model at the CCIA. This has been completed and the dosing of the *in vivo* model has now commenced. One hurdle likely to be encountered is the need to design species-specific beta III tubulin constructs to conduct toxicology studies in relevant species. This has been factored into the timeline.

| *Tribetarna*™ | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Milstones** | **2012** | | **2013** | | | | **2014** | | | |
| | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| Knockdown βIII tubulin in tumors *in vivo* | ▶ | | | | | | | | | |
| βIII tubulin ddRNAi as co-therapy | | ▶ | | | | | | | | |
| Vector production | | | ▶ | | | | | | | |
| Pre-pre IND / scientific advice EMA | | | ▶ | | | | | | | |
| Toxicology / biodistribution | | | | ▶ | | | | | | |
| IND preparation | | | | | ▶ | | | | | |
| | | | | | | | | | | |
| Clinical trial | | | | | | | | | ▶ | |

# Hepatitis B

## The Market

More than 2 billion people are infected with the hepatitis B virus (HBV) worldwide and an estimated 350 million are chronic carriers. HBV causes serious liver disease and every year about one million people worldwide die from chronic HBV infection, cirrhosis or HBV-induced liver cancer. There is no cure.

## Benitec's program and current status

Together with the respected China-based company Biomics Biotechnologies, Benitec Biopharma has identified and filed patents on more than 20 effective RNAi sequences that can silence the HBV polymerase gene. Through recent further evaluation and development we have selected the three most effective for incorporation into a single construct, and are optimizing their expression, using a series of promoters of varying activity. This "triple cassette", named *Hepbarna*™, will be tested in a preclinical model of HBV in China in the second half or 2012, and ultimately will be tested in a China-based clinical trial of hepatitis B virus-infected patients. Benitec has had some previous experience in utilizing ddRNAi for hepatitis through its association with sub-licensee, Tacere Therapeutics, who, with substantial input from Pfizer, have extensively developed and tested a ddRNAi construct targeting hepatitis C. It is anticipated that many of the lessons learned through that program will ensure that Benitec Biopharma's HBV program will be able to be significantly expedited as a result.

At the May 2012 CIG meeting, Professor York Zhu, President and CEO of Biomics Biotechnologies along with Dr Michael Graham, provided the following update to the Board on the status of the program:

"Our hepatitis B program is on track to deliver its expected outcomes. Several research scientists at Biomics Biotechnologies are working on this program to ensure that it meets it milestones. Based on the previous data we obtained, identifying several effective siRNA sequences utilizing Biomics' proprietary EsT screening technology, we have recently completed testing and have defined a number of highly effective ddRNAi molecules to knock down the HBV polymerase gene *in vitro* (Figure 5). In the last few months we have conducted a series of complex molecular manipulations of components of the DNA constructs to avoid potential adverse side effects; this was based on advice from Tacere Therapeutics' Director of R&D, Dr David Suhy. Furthermore, the research group has achieved nearly 100 per cent delivery of the molecules to the liver from a single intravenous injection in an animal model, confirming the feasibility of Benitec's therapeutic approach for this disease. Testing of constructs in a transgenic mouse model is due to commence within the next two months."

**Hear Dr York Zhu describe the HBV program here: http://www.youtube.com/watch?v=ld6IG-qIoMI**

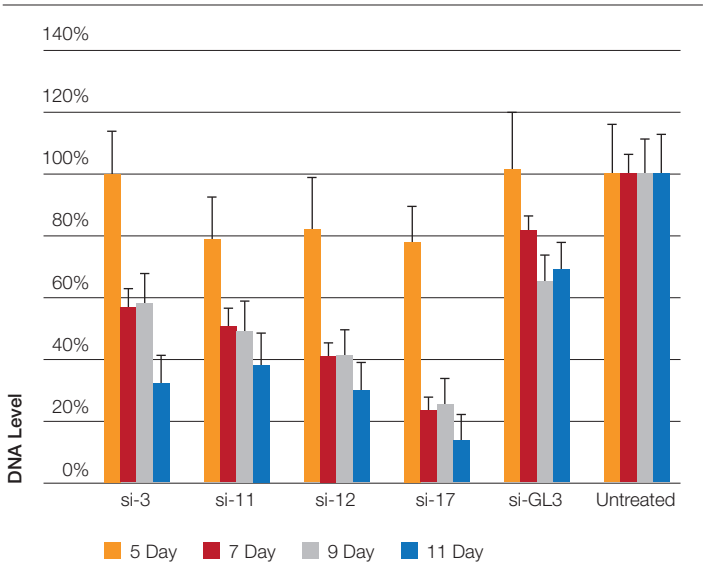



**Figure 5.** Efficacy of identified siRNA sequences to reduce production of HBV DNA in HepG2.2.15 cells that normally produce the virus. Four siRNAs (3, 11, 12 and 17) substantially decrease HBV replication. GL3 is an irrelevant siRNA control.

## Projected Timeline for the *Hepbarna*™ program

| *Hepbarna*™ | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Milstone | 2012 | | 2013 | | | | 2014 | | | |
| | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| Preliminary *in vivo* and *in vitro* validation of triple cassette | ▶ | | | | | | | | | |
| Optimising triple cassette | | | ▶ | | | | | | | |
| Final *in vivo* validation | | | | | ▶ | | | | | |
| AAV manufacturing | | | | | | ▶ | | | | |
| Toxicology and biodistribution studies | | | | | | | ▶ | | | |
| Characterisation of the vector and manufacturing process | | | | | | ▶ | | | | |
| SFDA filing | | | | | | | | | ▶ | |

# Oculopharyngeal Muscular Dystrophy

## The disease

Oculopharyngeal Muscular Dystrophy is a rare (affecting 1 in 100,000 people worldwide) form of muscle wasting that begins to cause symptoms in people typically between the ages of 40 - 70. The condition causes great difficulty with swallowing, surgery is of little assistance and the disease is often fatal. The disease arises as a consequence of a genetic mutation in the Poly (A) Binding Protein Nuclear 1 (PABPN1) gene. The affected muscles are localised around the throat, and therefore are an accessible target for delivery of a gene therapy therapeutic.

## Benitec Biopharma's program and current status

Benitec Biopharma is working with Professor George Dickson at the Royal Holloway, University of London who, in collaboration with researchers Dr Capucine Trollet and Professor Gillian Butler-Browne at the Paris-based Institut de Myologie (a reference centre for muscle disorders in France,) has access to significant scientific and clinical resources in this area, including human cells grown *in vitro* and an *in vivo* laboratory model of the disease.

We propose to develop a gene therapy strategy based on ddRNA interference to silence the expression of the mutant PABPN1 allele in muscle cells of OPMD patients. OPMD is particularly adapted to gene therapy since targeted cells are limited, the genetic mutation is small, known and located on a relatively small gene. Development in viral gene therapy vector options has made it feasible to consider gene therapy approaches for dominant inherited disorders such as OPMD.

It is planned to use an adeno associated viral vector to deliver the DNA directly to the affected swallowing muscles. Another possible therapy is to transform patients' muscle stem cells using a lentivirus expressing ddRNAi to silence the mutant gene, then transfer those stem cells to the affected swallowing muscles.

## Current status:

At the May 2012 CIG meeting, Professor George Dickson provided the following update to the Board on the status of the program:

"Despite only commencing the program with Benitec Biopharma in January this year, significant progress has already been made. ddRNAi constructs expressing multiple shRNA sequences have been made and are being tested. To date, single ddRNAi constructs produce around 65% gene knock down *in vitro*, when delivered using both lentiviral vectors and AAV. Furthermore, preliminary *in vivo* studies demonstrate encouraging levels of normal PABPN1 gene expression in muscles from AAV-delivered gene constructs. This is an excellent start to the program. Pre-clinical *in vitro* and *in vivo* studies proving the safety and efficacy of the constructs are both planned and in progress."

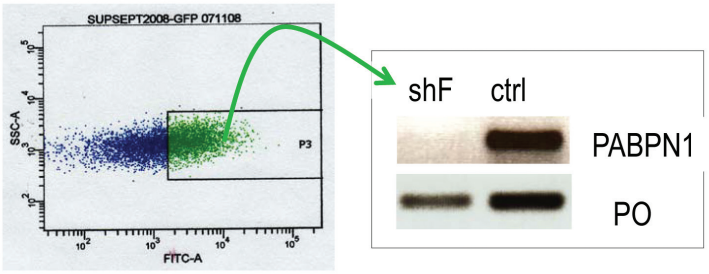



**Figure 6.** FACS-sorted ddRNAi transfected cells in culture showing around 95% decrease in the target PABPN1 protein.

Benitec Biopharma and Professor Dickson along with his Institut de Myologie colleagues Dr Trollet and Professor Butler-Browne are on track to commence pre-clinical studies in OPMD therapy in 2012 and is aiming to begin the first human clinical trial around 2014-15.

*CEO Dr Peter French commented: "We think this is going to be a tremendous opportunity to demonstrate the use of our technology to treat and potentially cure a currently incurable genetic disease."*

**Hear Professor Dickson speak about the program here: http://www.youtube.com/watch?v=v9oxx7lidOo**

# HIV/AIDS (sub-licensed to Calimmune, Inc)

## The Disease

AIDS is caused by the human immunodeficiency virus (HIV) that infects the patient's immune cells. Drug regimes can provide long term suppression of the disease, but these require an onerous and continuous daily regimen of drug consumption. One of the major concerns currently with HIV/AIDS therapeutics is that there are significant toxicities associated with current drug therapies. Most importantly, these drugs keep the virus in check but they don't cure the patient, the patient must continue to take them for life. Also, drug resistant strains of HIV emerge and there are no alternatives for patients with such strains. ddRNAi offers an alternative long term treatment and potential cure from single or limited treatments.

In February 2012 Benitec Biopharma and California-based Calimmune, Inc. completed a sub-licensing agreement for Calimmune to utilise ddRNAi to target up to three genes in HIV. This fulfilled Benitec's goal to leverage off the previous positive data from the US-based City of Hope HIV/AIDS-related lymphoma trial, which Benitec supported and was concluded in 2010.

The data from that trial provided the first clinical evidence that Benitec's patented ddRNAi approach is safe to use in human subjects and has the potential to deliver long-term gene silencing and positive clinical outcomes. City of Hope researchers believe long-term expression of this gene silencing could lead to a cure for HIV one day.

In May 2012, Professor John Rossi, City of Hope National Medical Centre, California USA provided the Board of Benitec Biopharma with an update of the City of Hope clinical trial follow-up:

"We are very encouraged by the good results to date from our work with Benitec and their ddRNAi approach, which we are using for the treatment of HIV infection. The trial we conducted in 2008-2010 and treated patients with HIV-related lymphoma. In a slight modification of their lymphoma treatment, blood stem cells from the patients were isolated and anti-HIV constructs introduced into the cells using a lentiviral vector. When the cells were reinfused into the patient they gave rise to differentiated immune cells which are inherently highly resistant to HIV infection. We have been monitoring these patients for over 3.5 years now, and there is still detectable expression of the ddRNAi construct. There were no adverse effects seen on the patients who received this treatment. The trial demonstrated that this approach to transform patients' stem cells long term using a ddRNAi construct targeted at a key HIV gene is safe and feasible, and provides the basis for transformational therapeutics in HIV.

"We've saved the lives of 3 of those 4 patients, three of them with this stem cell gene therapy modification. All of them have suppressed HIV loads. So basically this feasibility study has opened the door for this treatment approach and we think that it is a possible way of curing HIV by supplying stem cells that will give rise to blood cells resistant to HIV infection and eventually the viral blood cells will run out and the patient will be cured. That's our goal."

The positive result of the trial to determine safety and feasibility of lentivirus-transduced stem cell immunotherapy in patients undergoing autologous transplantation was published in Science Translational Medicine in June 2010.

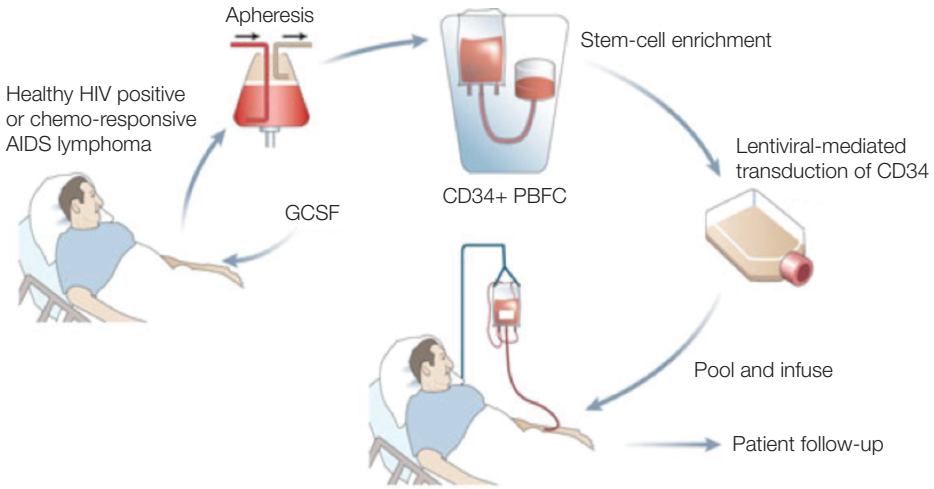
The data showed no overt toxicity associated with the process and persistent levels of shRNA expression were observed in two patients up to 24 months after the clinical procedure. The data also showed evidence of differentiated cells from transfected progenitor cells carried the ddRNAi construct.

## The Future

These results support the development of an RNAi-based cell therapy platform for HIV, and support the safety of Benitec's ddRNAi technology in humans. Furthermore, they provide evidence for the potential for stem cell-based therapies to provide long lasting or even permanent HIV viral control. Benitec Biopharma is excited to have licensed this program to Calimmune so that the potential of ddRNAi-modified hematopoietic stem cells to treat and ultimately cure HIV/AIDS can be realized. Calimmune have indicated that they are aiming to commence a clinical trial using ddRNAi in HIV patients this year.

**Hear Professor Rossi describe the ddRNAi approach here: http://www.youtube.com/watch?v=9XqJyYrYgwU**

**Figure 7.** Schema showing the process of the clinical trial conducted by the City of Hope in HIV/AIDS related lymphoma patients who received an autologous transfusion of transfected stem cells containing a construct expressing a shRNA targeting a key HIV gene.



# Hepatitis C (sub-licensed to Tacere Therapeutics)

## The Disease

Hepatitis C virus (HCV) infects 170 million people worldwide. It is a leading cause of cirrhosis, hepatocellular carcinoma and liver transplantation. Current hepatitis C drug regimens require injections of interferon, which causes severe flu-like symptoms and cannot be tolerated by some patients. ddRNAi offers the potential for a single, once-only injection which provides a curative treatment for this disease.

## The Market for New Therapeutics

There is considerable interest from multinational pharmaceutical companies in curative approaches to hepatitis C. As an example, in November 2011, Gilead Sciences Inc acquired US-based Pharmasset Inc for $11 billion. Pharmasset were developing an oral therapy for HCV, which had entered the clinic. However data in February 2012 showed that most of the patients on the trial relapsed after four weeks. The approach that Tacere is taking with a ddRNAi-based therapeutic is potentially a curative approach.

## Tacere Therapeutics

Benitec has had a long association with Tacere Therapeutics, a US-based privately held company who are developing a ddRNAi-based therapeutic to HCV under exclusive sublicenses provided by Benitec. Between 2007 and early 2012 Tacere worked closely with Pfizer on extensively developing this program through preclinical and IND-enabling studies.

Dr David Suhy, Director of Research and Development at Tacere Therapeutics provided the following project update to the Benitec Biopharma Board at the CIG meeting in May:

"Tacere Therapeutics has been developing TT-034, a ddRNAi-based HCV therapeutic for the last eight years, most recently in conjunction with Pfizer, who have invested significant financial and other resources in the pre-clinical development of the program. TT-034 comprises a recombinant AAV genome that is packaged within an AAV capsid. The expression cassette contained within TT-034 has been engineered to encode three independently expressed short hairpin RNAs (shRNAs) that target three well-conserved regions of the HCV genome and its therapeutic potential has been validated in several *in vitro* studies using replicon systems as well as an infectious tissue culture model of HCV. Pre-clinical experiments revealed that the use of AAV vectors results in the delivery and long-term expression of the HCV-specific shRNAs in almost 100% of hepatocytes (liver cells), where the virus replicates, from a single intravenous injection. *In vivo* testing of TT-034 in non-human primates results in durable, long term production of therapeutic quantities of each of the shRNAs with a complete absence of toxicity, even when dosing concentrations were administered up to 10-fold higher than what is predicted to be efficacious. The data are soon to be published in a scientific journal."

The program has progressed to the point where an IND submission is in preparation, and a substantial portion of clinical trial material has been manufactured. Advanced discussions have been held with the FDA. A US-based clinical trial of TT-034 is therefore possible to start as soon as early 2013, which would have a significant potential benefit for Benitec Biopharma as a clinical demonstration of the safety and efficacy of ddRNAi-based therapies. However, as a result of Pfizer closing its Sandwich (UK) facility, the timetable for the clinical development of TT-034 is unclear. Tacere's management is pursuing other partnering options for the program and Benitec Biopharma's management is in close communication with Tacere to determine the optimal path forward for this key program.

**Hear Dr Suhy describe the HCV program here:**
**http://www.youtube.com/watch?v=y9gX2HjfCgk**

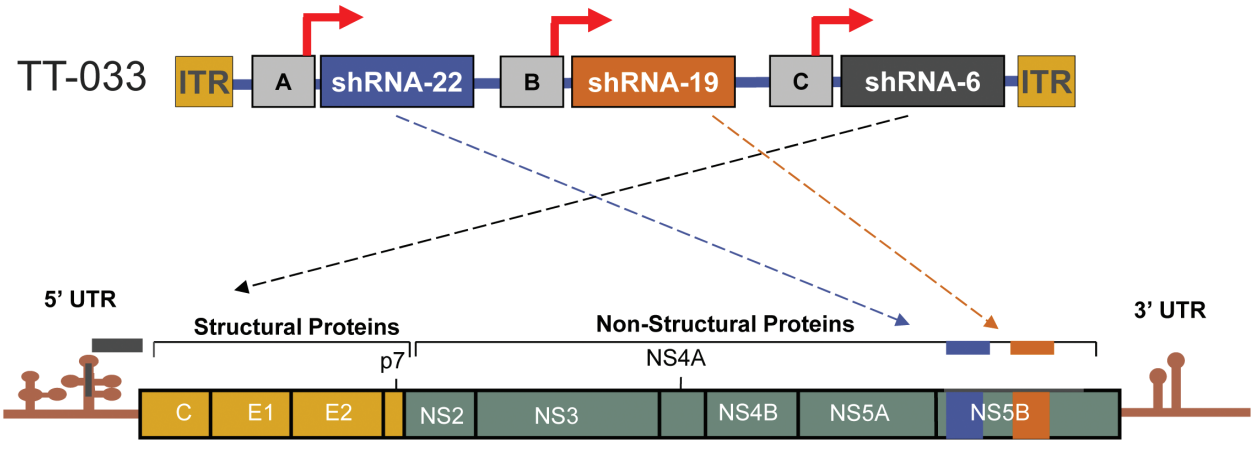
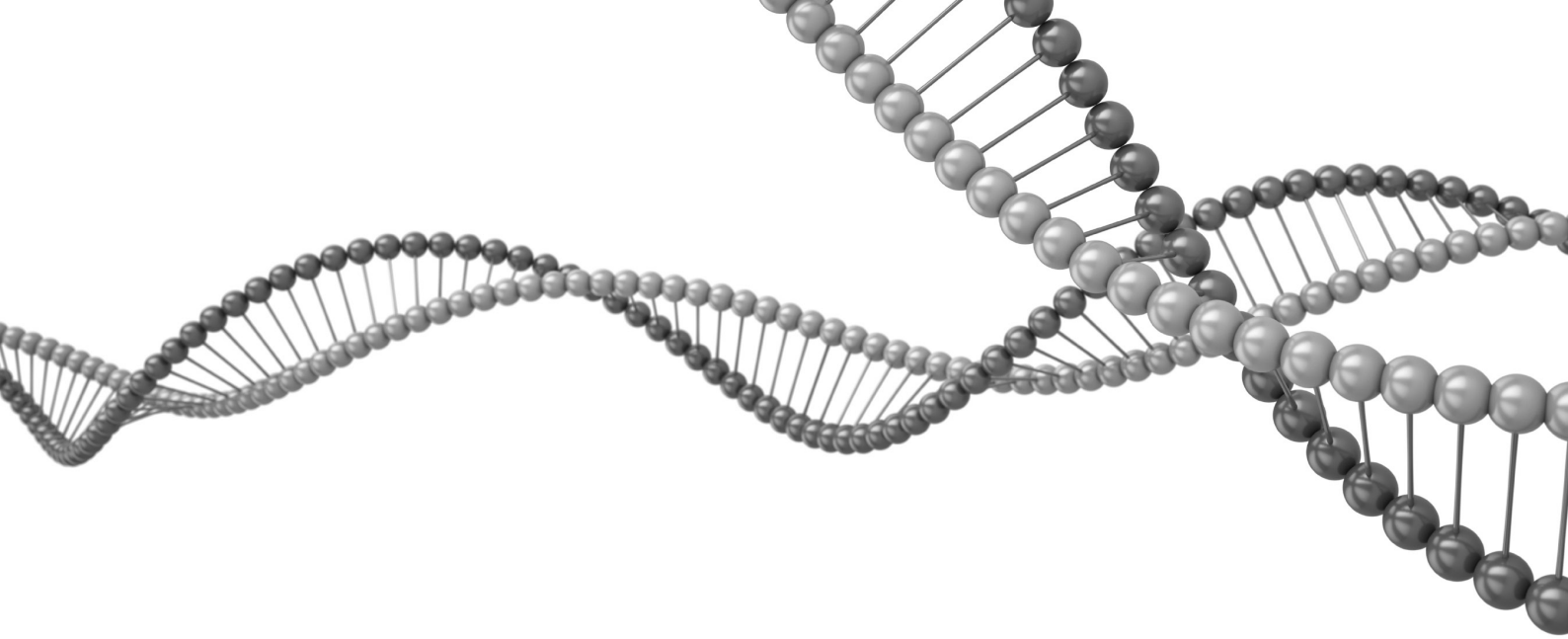



**Figure 8.** Diagrammatic representation of Tacere's therapeutic ddRNAi construct. The "triple cassette" construct is shown at the top. This consists of three individual cassettes which express three shRNAs (22, 19 and 6) cloned into an AAV vector. A genetic map of the HCV genome is shown below this; the individual shRNAs target different regions for silencing.



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For a list of Benitec's key patents and other information on the technology, the Company and the programs, please visit our website: www.benitec.com

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