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ASX ANNOUNCEMENT

Benitec's gene silencing technology demonstrates significant efficacy in a preclinical lung cancer model

- **ddRNAi provides significantly increased survival in an *in vivo* model of lung cancer**
- **UNSW patent on targeting beta III tubulin with gene silencing allowed in China**
- **Benitec commences discussions with a CRO to prepare for regulatory meetings**

Sydney Australia, 4 April 2013:

Benitec Biopharma reported data demonstrating the use of gene silencing to significantly increase the effectiveness of chemotherapy in a preclinical model of non-small cell lung cancer (NSCLC). The work was done with Benitec Biopharma's research collaboration partner, the Children's Cancer Institute Australia (CCIA), University of New South Wales, Sydney, Australia (UNSW).

The data showed that, in a mouse orthotopic model of human lung cancer, the animals that were treated with a combination of Tribetarna™ (the Benitec-designed ddRNAi silencing molecule targeting the beta III tubulin gene) and chemotherapy survived significantly longer than those that were treated with chemotherapy without the active ddRNAi molecule.

The CCIA researchers have demonstrated previously that the gene target of the silencing molecule, beta III tubulin, is strongly associated with the resistance of NSCLC tumours to chemotherapy[1].

According to Professor Maria Kavallaris of CCIA, the principal investigator on the collaboration, the data were obtained in an i*n vivo* orthotopic model that closely mimics the human situation. "The human lung cancers used in the model are strongly resistant to chemotherapy, and we were able to demonstrate that intravenous administration of Tribetarna™, in combination with cisplatin, a standard chemotherapy drug, was able to significantly ($p<0.02$) extend the survival of the animals when compared to control animals," Professor Kavallaris reported.

After sixty days, 50% of the mice in the group with the active ddRNAi construct were alive compared to only 14% in the control group.

"This is the first study to demonstrate that a ddRNAi approach can potently silence beta III tubulin expression and increase chemosensitivity *in vivo*, highlighting this as a potentially very promising treatment strategy for drug resistant NSCLC," she added.

Benitec's CEO, Dr Peter French commented: "Advanced stage lung cancer is associated with a very poor prognosis due to rapid acquisition of chemotherapy resistance by the tumor cells. Unfortunately, current treatment regimens have had only a modest effect on the course of the disease. Genetic therapy using ddRNAi to silence the beta III tubulin gene represents a novel approach to overcoming this resistance, and thus a potential game changer in the treatment of this highly fatal disease."

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[1] McCarroll JA, Gan PP, Liu M, Kavallaris M. βIII-Tubulin Is a Multifunctional Protein Involved in Drug Sensitivity and Tumorigenesis in Non–Small Cell Lung Cancer *Cancer Res*; 70(12); OF1–9.

Dr French further stated, “Whilst many early-phase clinical trials have been conducted using gene therapy for various malignancies with good safety profiles, there has been relatively limited efficacy demonstrated. One of the key reasons for this is the difficulty of delivering the therapeutic molecules to the target tissue. Gene delivery efficiency is an important requirement for successful gene therapy. The program has successfully overcome this hurdle through the preclinical use of Jet-PEI®, which the CCIA team has demonstrated is capable of delivering Tribetarna™ to the tumor cells in the lung, with very high specificity and no apparent or gross adverse effects.”

The UNSW patent application covering the use of RNA interference to silence the beta III tubulin gene for overcoming chemotherapy resistance was allowed in China last week. Lung cancer increased 465% in China over the past thirty years and is now China’s leading cause of cancer death[2].

Benitec Biopharma is in discussions with a US-based clinical research organization, Ground Zero Pharmaceuticals, to prepare appropriate documentation for preliminary discussions with regulatory authorities, in particular the FDA, around requirements for clinical trials for this unique combinatorial approach of a ddRNAi silencing construct and a chemotherapy agent in advanced non-small cell lung cancer patients.

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About non-small cell lung cancer:

Lung cancer is a very common disease worldwide. Lung cancer is classified into two types – small cell and non- small cell lung cancer (NSCLC). NSCLC comprises the great majority (~85%) of cases of lung cancer. Treatment depends on various factors, but may involve surgery, chemotherapy, radiotherapy or a combination thereof. Unfortunately, NSCLC eventually becomes resistant to these drugs, sometimes very rapidly. Late-stage NSCLC has a very poor prognosis and is the biggest cause of cancer-related deaths globally.

About Benitec Biopharma Limited:

Benitec Biopharma Limited is an ASX-listed biotechnology company (ASX Code: BLT) based in Sydney, Australia. The company has a pipeline of in-house and partnered therapeutic programs based on its patented gene-silencing technology, ddRNAi. Benitec is developing treatments for chronic and life-threatening human conditions such as Hepatitis C, Hepatitis B, wet age-related macular degeneration, cancer-associated pain, drug resistant lung cancer and oculopharyngeal muscular dystrophy based on this technology. In addition, Benitec has licensed ddRNAi technology to other biopharmaceutical companies who are progressing their programs towards the clinic for applications including HIV/AIDS, retinitis pigmentosa and Huntington’s disease. For more information on Benitec refer to the Company’s website at www.benitec.com.

Since 2009, Benitec and CCIA have been collaborating on a project using their joint IP to exploit the use of ddRNAi to silence βIII-tubulin in NSCLC with the aim of taking this to a clinical trial. The aim of this project is to obtain proof of concept that vector-expressed RNAi (in the form of a multi-promoter multicassette vector) and delivery systems provided by Benitec will provide effective delivery of βIII-tubulin RNAi that results in sustained knockdown of βIII-tubulin expression in NSCLC cells and tumours *in vitro* and *in vivo.*

[2] Zhao P, Dai M, Chen W, Li N. Cancer trends in China. *Jpn J Clin Oncol* 2010;40(4)281–285