

## NEWS

### **BENITEC PROVIDES ADDITIONAL CONTEXT ON RNAi STUDY PUBLISHED IN NATURE**

**May 25, 2005, Mountain View, California** – Benitec Ltd. (ASX: BLT), a leading developer of RNA interference (RNAi)-based therapeutics, today provided additional context and guidance with respect to a paper published in the journal *Nature*. In the *Nature* paper, Mark Kay, M.D., Ph.D., Professor of Pediatrics and Genetics at Stanford University School of Medicine and Chairman of Benitec’s Scientific Advisory Board, published the findings of his laboratory regarding the potential underlying toxicity associated with overdosing mice with short hairpin RNA (shRNA). The study, entitled “*Fatality in mice due to oversaturation of cellular microRNA/short hairpin RNA pathways*,” was intended to test the limits of RNAi expression with respect to safety and efficacy and to serve as a guide for drug development within this new therapeutic modality.

Dr. Kay stated, “It is extremely important that the results of this study are not misinterpreted—the paper should in no way dampen the enthusiasm for RNAi therapeutics. The relevance of the study is that it provides insights into the mode of action of RNAi as well as the mechanism of toxicity; and to understand the safety limits this early on is invaluable to RNAi drug development efforts. It is also important to point out that, as published in the paper, we found effective and safe shRNA sequences that when administered at therapeutic doses were able to achieve safe, long-term down-regulation of important disease targets such as Hepatitis B.”

Sara Cunningham, Chief Executive Officer of Benitec, stated, “Dr. Kay and our scientists have worked closely over the last several years to elucidate the potential toxicities of RNAi therapeutics. Although RNAi is a natural phenomenon that exists in every cell of the human body, as we learn to use this existing mechanism as a powerful means of fighting disease, we must also understand what happens within the cell as we do so. In designing our approach to treat Hepatitis C, we came across sequences that were toxic and therefore were rejected for further development. It is important to note that all RNAi molecules, just as all drugs, are toxic at sufficiently high doses, and the key for effectiveness is to find the appropriate therapeutic window, as we have, in which drug candidates are safe and effective with an acceptable side effect profile. It is also important to recognize that in order to study RNAi-mediated toxicity, the mice in Dr. Kay’s study were dosed at significantly higher levels than those with which we have shown efficacy in destroying the Hepatitis C virus in a similar animal model.”

John Rossi, Ph.D., Director of the Department of Molecular Biology and Dean of the Graduate School of Biological Sciences of the Beckman Research Institute of the City of

Hope, and Principal Investigator on the RNAi HIV/AIDS therapy being co-developed with Benitec, stated, “These studies in animals are important for all applications of RNAi since they show, not unexpectedly, that exceptionally high dosing of shRNAs and subsequently siRNAs can saturate components of the RNAi pathway leading to reductions in mature micro RNA levels and ultimately to toxicity. The take home message here is to carefully test the expression or dosing of sh/siRNAs for any potential clinical application in a relevant cellular or animal model. Work in our lab as well as that of others has shown that long term expression of shRNAs targeting HIV in primary human and simian hematopoietic stem cell derived blood cells have no deleterious consequences on hematopoietic cell viability either in culture or in animals while still achieving therapeutic doses.”

### **About Benitec**

Benitec is an international biotechnology company focused on developing therapeutics to treat serious diseases using its proprietary RNAi technology. Benitec is listed on the Australian Stock Exchange and has its operations in Mountain View, California, USA. Its lead therapeutic programs are for Hepatitis C Virus (HCV) and the Human Immunodeficiency Virus (HIV). Benitec’s RNA-based HIV therapeutic, co-developed with the Center for Biomedicine & Genetics at the City of Hope in Los Angeles, California, will enter Phase I clinical trials in 2006. Benitec’s RNAi therapeutic for HCV will enter clinical trials in 2007. For additional information, please visit [www.benitec.com](http://www.benitec.com).

### **Forward-looking Statements**

*This press release contains forward-looking statements that reflect the Companies’ current expectations regarding future events. Forward-looking statements necessarily involve risks and uncertainties. Actual events could differ materially from those projected herein and depend on a number of factors including the success of the Companies’ research strategy, the applicability of the discoveries made therein, the successful and timely completion of clinical studies and the uncertainties related to the regulatory process.*

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