ASX RELEASE

Benitec Pain Program Receives Clinical Endorsement and Moves Towards the Clinic

Summary:

- Strong endorsement of Pain Program from US and European clinical pain specialists
- Appointment of Californian-based CRO to manage the clinical approval process with the USFDA
- Appointment of in-house regulatory compliance officer
- Engagement of internationally recognised pre-clinical organisation to expand laboratory program
- Appointment of Benitec's founding scientist to manage the program
- CEO to present Pain Program strategy to clinicians and industry leaders at a major Pain Summit in San Francisco this week

Sydney, Australia. Benitec Ltd (ASX:BLT) a world leader in RNA-based gene silencing for human therapeutics, has taken significant steps in a coordinated strategy to fast track the pre-clinical, clinical and commercial development of its lead program – a novel gene silencing therapeutic for intractable cancer-associated neuropathic pain.

Campbell Alliance Group Inc. (an inVentiv Health company and the leading management consulting firm specializing in the pharmaceutical and biotech industry) has completed the first stage of a commercial evaluation engagement, with very encouraging results. In this first stage, Campbell Alliance undertook an assessment of the positioning and market potential for Benitec's ddRNAi product in the cancer-associated pain market, which was estimated at being worth $3.1 billion in the US alone in 2009[1]. This was done with substantial input from interviews with nine leading pain specialists (key opinion leaders or KOLs) in the US and Europe. The key findings of this analysis, include the following

- The pain specialists interviewed rated the overall attractiveness of the potential Benitec product highly due to its unique mechanism of action and its potential for minimal toxicity.
- The potential for the product to treat neuropathic pain was seen by interviewed KOLs as especially beneficial, as it might avoid the side effects and other limitations of opioids and other current treatments.

[1] Source: WWMR Inc, 2009

- The report estimated the revenue potential of the product for terminal cancer pain patients in the palliative care setting alone to be approximately $600 million p.a**.** This estimate was based on analog pricing considerations and potential utilization rates across the major tumor indications as reported by the KOLs interviewed.
- The KOLs also suggested that indications beyond cancer pain could potentially also be targeted for this product, increasing its potential usage and therefore its potential revenue. Examples mentioned included shingles and diabetic neuropathy.

“These findings validate our pain program directly from the pain clinicians themselves” said Dr French. “It reinforces our focus on the pain program, and provide the impetus for Benitec to mobilize additional resources to the program and to progress to the next stage of Benitec’s commercial outreach for this program in the US and Europe with Campbell Alliance.”

In addition, Benitec has appointed US-based Ground Zero Pharmaceuticals as the CRO to advance the pain program into clinical testing under a USFDA-approved protocol. At the same time, Benitec has added to its in-house capability by appointing a regulatory compliance officer, Ms Mariam Ajaj, to work with GZP.

Benitec have also contracted internationally recognised TetraQ, based at the University of Queensland to undertake pre-clinical testing required to produce data for the regulatory process. GZP have worked with TetraQ on other projects in the past, ensuring solid lines of communication and a functional/constructive working relationship are in place. Benitec’s founding scientist, Dr Mick Graham, is supervising this aspect of the project, as a consultant to Benitec.

Dr French summarised Benitec’s strategic thinking in this area. “Although the pain program is at an early preclinical stage, we are aware of the significant unmet clinical need for a product with the unique features of our technology, and therefore we are seeking to fast track its development. I believe this is a unique opportunity for Benitec to demonstrate the power and potential of our gene silencing technology in both clinical and commercial settings over the next 12 months.”

As part of the Company’s business development strategy, Benitec’s CEO, Dr Peter French, will present a poster (see attached) on Benitec’s gene silencing approach to a novel treatment for neuropathic pain at the 5th Annual Pain Summit in San Francisco on 21st September.

For Further Information

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About Benitec www.benitec.com

Benitec Limited is developing novel treatments for chronic and life-threatening conditions based on gene silencing using a transformational technology, DNA-directed RNA interference (ddRNAi) - sometimes called expressed RNAi. The technology's potential to address unmet medical needs and, potentially, to cure disease results from its demonstrated ability to permanently silence genes which cause the condition.

Benitec now either owns or exclusively licences from CSIRO more than 40 granted or allowed patents in the field of RNA interference for human therapeutic applications. Patents have been granted in key territories such as the USA, the UK, Japan, Europe, Canada and Australia. In addition, Benitec has almost 50 patent applications pending for which it is the owner or exclusive licensee from CSIRO, and has further intellectual property under development as a result of its pipeline program.

Benitec trades on the Australian stock exchange under the symbol "BLT". The Company was founded in 1997 and has been publicly held since 2001. The Company aims to deliver a range of novel ddRNAi-based therapeutics to the clinic in partnership with the pharmaceutical industry. In-house it is pursuing a focused R&D strategy in infectious diseases, cancer and chronic cancer-associated pain, as well as programs with licensees that have advanced to pre-clinical and/or clinical trials.

A New Class of Pain Therapeutics - ddRNAi Gene Constructs

Peter French* and Michael Graham

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Abstract

The treatment of pain provides a significant market opportunity, estimated to be $30B per year and predicted to grow steadily in line with the demographics of aging. Despite this growing need, current therapies are unsatisfactory, with poor efficacy (typically 10-20% reduction in pain scores) and challenging safety profiles.

Current pain management is largely focused on opioids and derivatives thereof. A significant proportion of pain research and drug discovery/development is focused on targeting ion channel and Cox-2 inhibitors. Benitec's discovery and development program in chronic cancer-associated pain is focused on targets and mechanisms unrelated to opioids and has the potential to specifically and permanently inhibit a broad range of molecules known to be involved in pain.

Benitec's program utilizes DNA-directed RNA interference (ddRNAi, in which it has a dominant IP position) to permanently silence genes involved in mediation of pain signals in the central nervous system.

The objective is to develop a ddRNAi-based product containing a gene construct expressing an shRNA molecule specific for a gene for a molecule involved in transmission of pain stimuli to achieve long-lasting (weeks to months) pain relief.

A group of China-based researchers has recently published a proof of concept study that shows that this approach - a gene construct expressing an shRNA molecule - targeting PKCγ in a rat model of neuropathic pain, is both safe and effective [Zou *et al*, 2011]. There are a number of other potential gene targets within the spinal cord that lend themselves to this approach, and Benitec is also exploring these.

Benitec is developing and testing several shRNA constructs specific for a range of these potential human gene targets, confirming their activity *in vitro* and *in vivo* with the aim of utilizing the most effective constructs in a Phase 1 clinical trial, and ultimately to bring a new class of ddRNAi-based therapeutic pain molecules to the market.

About Benitec Ltd

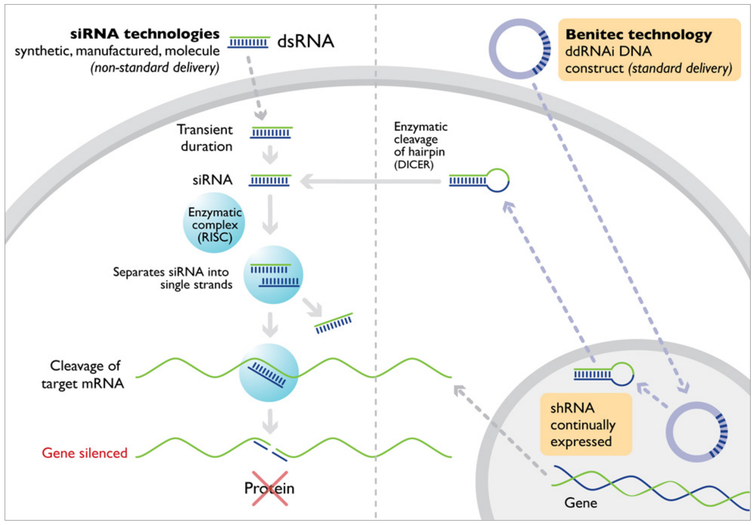
Benitec Limited is an Australian-based public biotechnology company developing novel treatments for chronic and life-threatening conditions based on a transformational technology, DNA-directed RNA interference (ddRNAi). The technology's potential to address unmet medical needs and, potentially, to cure disease, results from its demonstrated ability to permanently silence genes that cause the condition. Benitec holds the predominant patent position in the use of ddRNAi to silence genes for human therapeutic and research applications.

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, recently successfully reissued in the **US** and allowed in the **EU**, and granted broadly in other key jurisdictions including **Australia, Japan, South Africa, India, China, Canada and the UK**. This patent estate contains key claims covering methods for silencing genes by generating dsRNA inside a cell from a DNA construct.

Benitec collaborates with organisations globally to utilise its patent estate to develop novel gene silencing therapeutics for chronic life threatening diseases and disorders, particularly in **cancer and infectious disease**. Benitec is happy to explore collaborations and partnerships with research groups and pharmaceutical companies to further develop therapeutic products based on the power of ddRNAi.

About ddRNAi

The discovery of RNAi was awarded the Nobel Prize in 2006. Benitec's RNAi modality differs significantly from that of standard siRNA. Benitec's technology delivers **DNA coding for specific sequences of double stranded RNA** into the cell, which, after processing by cellular enzymes, interferes with mRNA and silences the target gene. The effect of this is to ensure that a specific protein is not made, with the result that the course of the target disease can be profoundly altered. This approach mimics the body's own machinery for fighting disease.



There are several advantages in choosing ddRNAi over siRNA: it can be delivered to target cells in an efficient manner using a proven viral-based gene delivery system; it offers the possibility of long-term stable shRNA expression by integrating into the chromosomal DNA; different target genes can be silenced using constructs that are engineered to yield multiple siRNA duplexes upon Dicer-mediated cleavage, and shRNA expression can be targeted to particular cell types or turned on at specific times through the use of tissue-specific or inducible promoters

The Concept – ddRNAi as a Pain Therapy

The Table lists several gene targets that have been demonstrated to be effectively targeted by RNAi in a range of animal models for pain therapy:

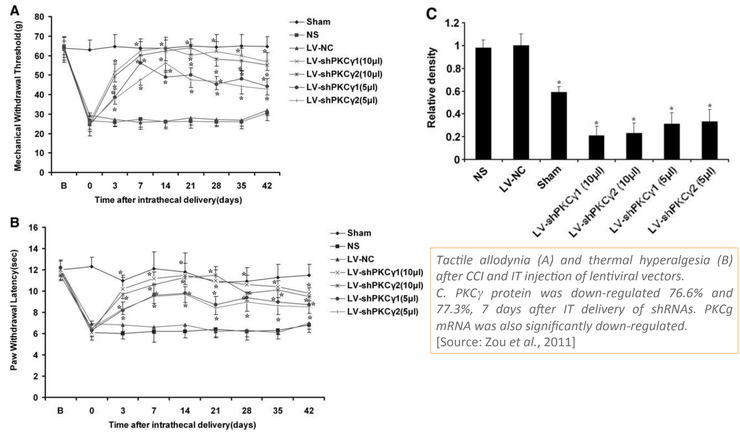
Target	RNAi Method	Type of Pain	Reference
ATP receptor P2X3	siRNA	neuropathic	Dorn *et al*, 2004
NMDA receptor NR2B	siRNA	spontaneous	Tan *et al, 2005*
NMDA receptor NR1	shRNA	mechanical allodynia	Garraway *et al*, 2007
MMP-2 & MMP-9	siRNA	mechanical allodynia	Kawasaki *et al, 2008*
K^+ channel Kir4.1	siRNA	neuropathic pain	Vit *et al, 2008*
Capsaicin receptor TRPV1	shRNA	mechanical allodynia	Christoph *et al*, 2008
EP receptor EP4 (prostaglandin E2)	shRNA	nociceptive	Lin *et al, 2006*
PKCγ	shRNA	neuropathic	Zou *et al, 2011*

The Target – Protein Kinase C gamma (PKCγ)

PKCγ is found mostly in the brain and spinal cord. Like other PKC family isoforms, PKCγ is thought to be an important second messenger in intracellular signal transduction. Inhibition of PKCγ in the spinal cord preserves acute pain but inhibits neuropathic pain (Malmberg *et al*., 1997), suggesting that it plays an important role in the development of central sensitization, especially in neuropathic pain after nerve injury. From a clinical perspective, the very restricted spinal cord location of the PKCγ-containing interneurons is advantageous (Malmberg *et al*., 1997). Development of specific inhibitors of PKCγ could provide solutions to alleviate neuropathic pain states without the profound side effects that are inevitable with nonselective inhibitors of PKC. ddRNAi provides that possibility.

Proof of Concept Study – Zou *et al*

A recent study by Zou *et al* confirmed the potential of this target for ddRNAi therapy. They designed replication-deficient, self-inactivating lentiviral vectors encoding shRNA constructs against the PKCγ gene, and observed the inhibitory effect of the shRNAs *in vitro* and *in vivo* (using IT administration of the constructs on chronic constriction injury–induced neuropathic pain in rats). Their results demonstrated that that intrathecal (IT) delivery of ddRNAi constructs PKCγ can alleviate allodynia and hyperalgesia without adverse side effects. Some of the data are shown below:

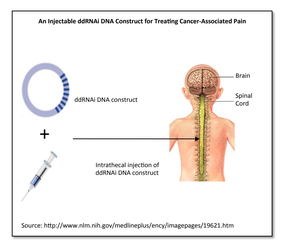


Tactile allodynia (A) and thermal hyperalgesia (B) after CCI and IT injection of lentiviral vectors.
C. PKCγ protein was down-regulated 76.6% and 77.3%, 7 days after IT delivery of shRNAs. PKCg mRNA was also significantly down-regulated.
[Source: Zou *et al.*, 2011]

"These results support the potential use of shRNA expression vectors as a gene therapy approach to neuropathic pain."
- Zou et al, 2011.

Next Steps

Benitec's scientists are designing and testing a range of ddRNAi constructs against PKCγ and other potential targets localised within the spinal cord for their safety and efficacy as novel pain therapeutics. The initial target patient group includes terminally ill cancer patients with intractable neuropathic pain.



Conclusion

The studies to date indicate that **ddRNAi**, used to produce a long-term knockdown of gene expression in the spinal cord, can act as **a new class of pain therapeutic molecules, with a unique mechanism of action and potential for minimal toxicity**.
Benitec plans to develop its ddRNAi technology towards making this a clinical reality.

References

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