Firm Focuses Operations on Gene Silencing

By Carol Potera February 15, 2012

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Benitec Pits DNA-Directed RNA Interference against Chronic and Life-Threatening Diseases

Benitec, an Australian biotechnology company, holds a predominant patent position for silencing genes with DNA-directed RNA interference (ddRNAi). It is developing therapeutics to prove the validity of ddRNAi in treating cancer, infectious diseases, and disorders of the central nervous system.

"We want to demonstrate the applicability of the ddRNAi technology across the board," says CEO Peter French, Ph.D.

The company's tag line, "Silencing genes for life", summarizes the strengths of the technology compared to siRNA methods. siRNA therapeutics must be synthetically manufactured, are short-acting, and need to be replenished, similar to small molecule drugs.

researchers are still working to optimally deliver synthetic RNA," says Dr. French.

Michael Graham, Ph.D., invented Benitec's gene-silencing ddRNAi technology while working at CSIRO. Benitec either owns or exclusively licenses from CSIRO a patent portfolio currently comprising 40 patents related to ddRNAi for human therapeutic applications.

The ddRNAi platform focuses on the long-term downregulation of genes, making it suitable for targeting chronic life-threatening diseases. "We are silencing genes instead of introducing new genes, which separates us from traditional gene therapy companies," Dr. French asserts.

The ddRNAi platform can be applied to a range of disease targets. Benitec chose a small number to confirm the potential of its technology.

The safety and proof-of-concept of ddRNAi was demonstrated in a Phase I trial in AIDS patients with lymphoma at the City of Hope research hospital. A short hairpin (sh) RNA construct (a single strand of RNA that folds back on itself expressed from a ddRNAi construct) was designed to target the tat/rev gene of HIV.

CD34+ cells from four patients were treated ex vivo with the shRNA construct and transfused. Two years later, three of the four patients continue to express the shRNA in their stem cells.

The results support the development of ddRNAi therapeutics for HIV. The City of Hope researchers have started a second trial using the same shRNA construct to further optimize the treatment.

Benitec scientists and colleagues at China-based Biomics Biotechnologies identified potential RNA target sequences to inhibit the replication of hepatitis B virus (HBV).

Cancer researchers at the Johns Hopkins University School of Medicine used a ddRNAi construct from Benitec to silence a key repair gene in prostate cancer cells. The prostate cancer cells are unable to survive after treatment with radiotherapy.

"This targeted treatment markedly enhanced the benefits of radiation therapy in both cellular and tumor models," the researchers concluded. Other radiotherapy-resistant tumors may benefit from the shRNAs created for the prostate cancer study.

Non-small-cell lung cancer (NSCLC) is the dominant type of lung cancer, and only about 15% of NSCLC patients survive more than five years. Benitec is developing a ddRNAi therapy to overcome chemotherapy resistance in human NSCLC cells. The gene targeted for silencing is beta III tubulin, and the firm reports that the ddRNAi construct significantly knocks down beta III tubulin in human lung cancer cells.

"By switching off the gene, cancer cells become more sensitive to cancer chemotherapy, both DNA-damaging agents like cisplatin and tubulin-binding agents like the taxanes," says Dr. French.

Comparison of modes of action between siRNA (short-term gene silencing) and ddRNAi (long-term gene silencing).

This will produce long-term pain relief potentially equivalent to that of opioid infusions. The exact role of PKCγ in chronic pain is unclear, but it appears to mediate pain signals from the periphery through the central nervous system.

A team of Chinese researchers showed the proof of concept of this approach in a preclinical model of pain. A single injection decreased the expression of PKCγ messenger RNA and protein and achieved a significant reduction in pain for at least six weeks without side effects.

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