



DNA-directed RNAi and the crown jewels

WHEN MERCK ANNOUNCED last year it was buying Sirna Therapeutics for over US\$1 billion, the world sat up and took notice. RNAi was now being seen as not only a revolution in our understanding but something with an unimaginable dollar value as well. One of those closely watching the saga was Australian biotech company Benitec, which holds extremely valuable IP in the other RNAi space, DNA-directed RNAi.

Benitec as a company has had a pretty chequered history, which has caused some damage to both its reputation and its share price, but what is beyond dispute is the value of its intellectual property portfolio. Benitec holds a number of important patents that provide a key technology to trigger RNAi in human cells. Its collaborator in the technology development, the CSIRO, holds the patents for its use in animals and plants.

There are two modes of delivery to effect RNAi – short interfering RNAs (siRNAs), which are synthetic and delivered as an oligo, and this is the area that Sirna Therapeutics and others work in. On the other side is DNA-directed RNAi (ddRNAi), in which a DNA construct is inserted into the cell using a variety of vectors. When expressed, these vectors trigger the production of double stranded RNA (dsRNA), which is then immediately cleaved into siRNAs, entering the cellular RNAi pathway and silencing the target gene. This is the area that Benitec holds key patents in.

It was predominantly the value of these patents that drew Sue MacLeman to the company in August last year. It was set up in 1997 to commercialise research from

the Queensland Department of Primary Industries, led by Dr Michael Graham and Dr Ken Reed. Back in 1997, RNAi was virtually unheard of. Mello and Fire's famous 1998 paper was in nematodes and it was not at that stage thought that RNAi worked in mammalian cells. Benitec's breakthrough was actually in the same year, when Graham and colleagues showed that DNA constructs could trigger RNAi in human and mammalian cells.

"ddRNAi is natural," MacLeman says. "It's a natural process because it is one that we have always had in our bodies. siRNAs are synthetic. The other big advantage of our technology over siRNAi is that we don't activate the cells' interferon or stress response and that's mainly because it is part of a natural cellular defense mechanism."

The Graham patent is now Benitec's crown jewel, MacLeman says, and is what made keeping the company going a worthwhile enterprise. "It has been a checkered history," MacLeman, originally a hospital pharmacist who has worked in pharma and biotech for many years, says. The company has a reputation as an enthusiastic litigant, something that MacLeman is now trying to extricate it from.

"We've still got ongoing litigation now as a result of that really sad time for the company," she says. "Instead of doing collaborations they took a more litigious view and they sued many people, to the cost of the company's reputation and finances. Back in 2004 they had started a number of projects, one with City of Hope (in California) in the area of HIV and that one is still ongoing. It is starting to go into humans, which is wonderful news for us."

The company has been in dire financial straits, from which it has not yet quite recovered, but MacLeman is confident of its future. It has a deal with Sigma-Aldrich and Pfizer, in which Sigma, an equity holder, has an exclusive licence to use Benitec's technology for reagents and for research use. Sigma is able to sub-license those applications with Benitec's approval. Pfizer is one of those sub-licensees from Sigma, from which Benitec earns a revenue stream. Benitec has a similar agreement with Merck.

In terms of clinical trials, it is working with City of Hope on stem cell therapy for HIV/AIDS lymphoma and T cell therapy for HIV/AIDS. It has licensed out a hepatitis C project to US company Tacere and is looking to further the technology in cancer and autoimmune diseases such as psoriasis.

"And we think we are going to be effective at lower doses," MacLeman says. "We have the ability to control the degree of silencing within the cells and we can deliver it in more than one way – it's quite useful to have a number of options. You can use a plasmid in a liposome or a viral vector – there's all sorts of ways. Delivery is a big issue for all companies.

"But if you think about the therapeutic areas that sit with this: out of the cancers you could have ovarian, breast or prostate; HIV; there's a whole lot of neurological disorders like Alzheimer's or Parkinsons; hep C, which we are working on, and a lot of others as well. But it's a matter of focus and choosing the right ones where we are able to position ourselves and make a difference." **ALS**

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