The Balmain biotech with 10 shots at billions, and one shortcut

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Benitec's applications inject DNA that aims to 'silence' genes which cause diseases, such as hepatitis C.

The journey from CSIRO test tube to US Food & Drug Administration approval is one that few medical technologies survive, but Balmain-based Benitec is trying ten different routes for its 'gene-silencing' treatment, including one potential shortcut through the FDA process.

That shortcut is the FDA's 'breakthrough therapy' (http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/ucm341027.l designation, which slashes the amount of data required for approval when treatments address a rare disease for which no other treatment is available, or can help sufferers of a disease for whom alternative treatments have failed.

A shortcut to monetisation would be welcome news for Benitec's investors, especially the mums-and-dads who've stuck with the company since its original ASX listing in 1997 and are lauded by Peter French, the CEO since 2010, as "visionaries" - albeit visionaries whose investment is, at September 30's share price of 45 cents, "deep under water".

Benitec's technology - which it is hoping might provide a one-shot cure for everything from Hepatitis C to AIDS - is called DNA-directed ribonucleic acid interference, or ddRNAi. It was patented in the 1990s by former CSIRO scientist Dr Michael Graham, who founded Benitec in 1997 and rejoined in 2012, the same year Benitec's patents were re-issued at the conclusion of lengthy litigation.

(For a fuller history of Benitec and a great layman's description of how ddRNAi is supposed to work, BRW recommends this wonderful Monthly piece (https://www.themonthly.com.au/issue/2014/october/1412085600/michael-lucy/dr-graham-s-patented-elixir)from 2014).

The next 18 months are critical in Benitec's 18-year rollercoaster ride, French tells BRW. Over his five year tenure he has already transformed Benitec from a company with $500,000 at bank, no labs and no clinical programs, to one with $40 million cash, a Nasdaq dual listing, a lab in San Francisco and clinical programs testing ddRNAi's effectiveness against 10 diseases globally.

The most advanced of these on paper is treating hepatitis C, where Benitec has just added a fourth site (http://www.asx.com.au/asxpdf/20150916/pdf/431c2hrndpmlg9.pdf) to its US trial. In classic biotech style, French hopes this trial can gather enough supportive data

Benitec CEO Peter French

that a big pharmaceutical company buys the application and undertakes the $500 million business of getting it through 'phase 3' FDA approval and on to the market. Wistfully, he points to the $US11 billion paid by Gilead in 2011 for Pharmasset, maker of a 12-week pill-based treatment for hepatitis C which is now the biggest-selling drug in the world.

However the hepatitis C application for ddRNAi might be beaten to commercialisation by an application Benitec is about to test for a rare form of muscular dystrophy called oculopharyngeal muscular dystrophy (OPMD).

Known as an 'orphan disease' because so few people suffer it - 3000 across the entire US - a successful treatment for OPMD could qualify for 'breakthrough therapy' status with the FDA, French says.

"We can get phase I/II data from 10 patients, and if the FDA is satisfied that it's safe and that there's no other treatment for the disease, we'd be able to take it to market ourselves."

This scenario has already played out for a Dutch gene therapy maker, UniQure, which received the European Union's equivalent of breakthrough status for Glybera, a one-shot treatment for an 'orphan' disease called familial lipoprotein lipase deficiency which effects about 200 people in Europe.

Each shot of Glybera is priced at $US1 million, although subsequent doubts about its efficacy from health authorities in some countries have made it less likely insurers will reimburse its cost (http://www.bloomberg.com/news/articles/2015-05-21/world-s-most-expensive-medicine-faces-first-test-in-germany), at least for now.

Benitec wouldn't charge anything like $1 million for a breakthrough-approved OPMD treatment, French says.

"We'd charge less than that to get it on to the market quickly. It could even be a break-even or a loss leader for us, just to show that this technology works - in the case of OPMD we can both turn off the mutant gene and put in a healthy gene - and announce to people that we've also got applications for hep C, hep B et cetera in the pipeline."

Benitec is working with London's Royal Holloway University and the French national reference centre for muscle disorders on the OPMD application, which will proceed to clinical trial once the construct to be injected is finalised.

Breakthrough approval for the hepatitis C application is also a possibility, French says, provided it was for sufferers for whom other available treatments have failed.

Any success for Benitec in getting an application approved, or a good enough bet for a deal with big pharma, will make the Australian majority of its 25 staff wealthy. However most of the sales revenue or royalties will flow to the US, as the bulk of Benitec's capital had to be raised there.

Ten American VCs were tapped for $30 million in 2014, because Australian VCs didn't know how to value the opportunity, French says.

"In America you can speak to venture capital analysts who have PhDs in RNA interference, you can get down to the nitty gritty and they get it," he says.

"In Australia we're the only gene therapy company, and we don't tick enough boxes. I find the VCs here would rather go for something like a medical device, where you can sterilise it and guarantee it's safe for everyone, you know the cost of manufacture, you know the margin, you know the distribution pathway – then they can value it!"

A side-benefit for Australia should a Benitec treatment be approved is that it's likely to be manufactured in Australia.

"If we do a deal with big pharma, as part of the package they want an assurance of supply, or at least a viable option for it," French says.

Benitec is already in discussions with the Victorian and South Australian governments around incentives to locate any manufacturing there.

“This would be a great, sophisticated replacement for their sunset industries, in my 35 year career as a cell and molecular biologist it’s the most complex science I’ve been involved with,” says French.

What’s injected in a Benitec application is a ‘viral vector’. The company’s scientists take a benign virus like AAV, strip out its DNA, put in DNA that creates the ‘gene silencing’ material, and uses the virus’s shell to take the DNA load where it needs to go.

FDA trials of the applications must skip the traditional ‘phase 1’ - where a treatment is tested in healthy people for safety - because the treatment alters the recipient’s genes in an irreversible way.

The enduring risk in gene therapy is that the injected DNA creates ‘silencing’ material that harms a gene essential to life. The whole industry went through a downturn in the 2000s after a small number of trials killed people.

For that reason the doses of viral vector in the hepatitis C trial so far have been so low, it’s known they won’t treat the disease in the recipients.

“Those people who’ve agreed to trial the first couple of dosage levels are heroes, because they know they will develop antibodies and won’t be able to receive the treatment again,” says French.

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