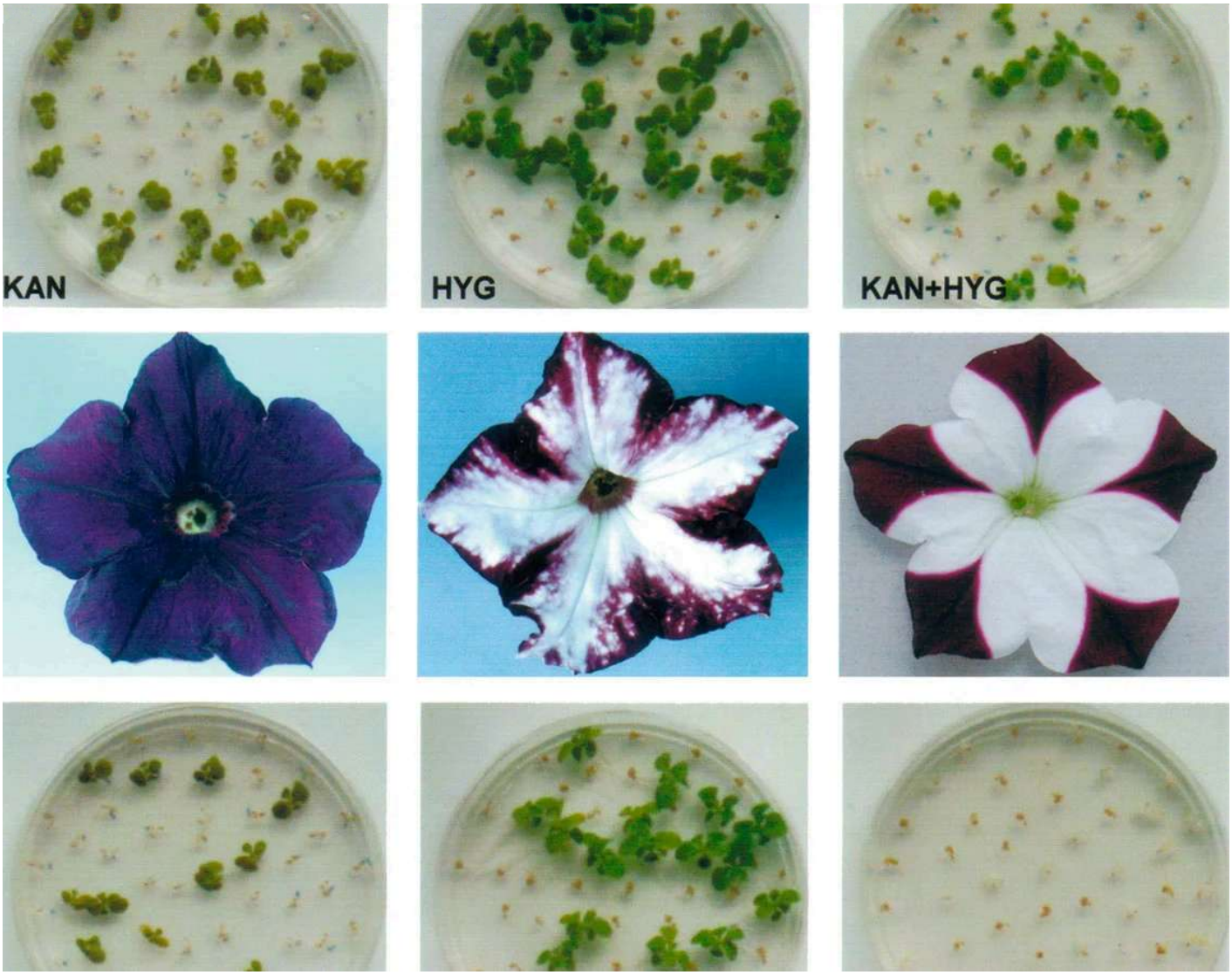
Dr Graham’s patented elixir

by Michael Lucy

Essays



Gene silencing, miracle cures and Balmain's biggest biotech company

Mick Graham was working at CSIRO's plant industry labs in Canberra in the 1990s, trying to genetically engineer virus-resistant potatoes, when he had his big idea about RNA interference. RNA is ribonucleic acid, DNA's less-famous sibling and a fundamental cog in the machinery of all living cells. RNA interference is one of the body's natural antiviral defence systems. Graham figured out how it worked, and had a few thoughts about how to use it for fighting disease. No one took him very seriously.

The next 20 years took Graham to Brisbane and Silicon Valley and back, through labs and courts and a strange landscape of corporations rising and falling and merging and dying, yo-yoing between academia and commerce and hope and despair with little recognition or reward. At long last, the scrawled loops and boxes and arrows of his notebook sketches – you can see them yourself, if you don't mind trawling through the archives of the US patent office – have almost become reality: a revolutionary method to treat mass killers like hepatitis C, lung cancer, HIV. *Almost* is the key word here: in science, you never really know until you do the experiment.

Graham began to explain his work to me over lunch in Melbourne on a blazing afternoon last summer. Benitec Biopharma Ltd, the small Sydney-based company built around Graham's patents, had arranged the meeting as part of its ongoing efforts to build a profile. "It's a drawback of being listed on the ASX," Graham told me later. "Communication strategies become very important. If you're a private company, you don't have to give a rat's arse."

Graham was affable and, like the rest of us – Carl Stubbings, Benitec's chief business officer, their PR guy and me – a little sweaty and dishevelled in the heat. I was there to get a sense of whether Benitec's grandiose claims were legit. "Just a gene jockey" was how Graham described himself, and he reminisced about working nearby in the late '80s. ("Florigene. Blue roses. Ring a bell?" I raised my eyebrows noncommittally.) He seemed ordinary enough. When it came time to tell his story, he started the way scientists often do when talking to laypeople, using "simple" terms and trying and failing to avoid condescension.

"You know the central dogma?" he said, watching closely for signs of understanding. "DNA makes RNA makes protein?" I nodded as sagely as I could.

Graham's patented breakthrough, he explained, was something called DNA-directed RNA interference (or ddRNAi). He described how it worked, and Stubbings interjected every so often to steer him back to concrete, comprehensible points: it's an entirely new kind of treatment; it's an Australian world-first; hepatitis C kills hundreds of thousands of people

smart. "That's not how the question phrases itself," he said. "The question is: why is everyone else so stupid?"

Graham's ddRNAi was also known as short hairpin RNA (shRNA). It was not to be confused with short interfering RNA (siRNA), a similar but less elegant approach patented by an American who, by the way, had won a Nobel prize in 2006 for his work. And yes, it seemed Graham had had a lot of arguments with CSIRO over who exactly discovered what when, not to mention a years-long intellectual property battle with a rival firm in the US courts. Oh, and no, ddRNAi-based treatments had not yet been trialled on actual humans. Animal results looked good, though, and the first human trials of a hepatitis C treatment called TT-034 would start soon.

Graham had done a fairly respectable job, I would later realise, of breaking down a tale of baffling scientific complexity and byzantine corporate machinations into something vaguely comprehensible to the non-specialist. The more I learnt, the less I understood.

The first human TT-034 test patient was injected at the end of May. "He came through fine," Benitec's CEO, Peter French, tells me. "No problems at all." Further tests have been delayed due to the difficulty of finding patients who meet the trial's stringent criteria, though French keeps a lid on his disappointment. "Not as much has happened as we would have liked … but the FDA [the US Food and Drug Administration] and the NIH [National Institutes of Health] are quite rightly concerned that we go carefully."

The hepatitis C virus settles in the liver, and over time destroys it. The World Health Organization estimates that about 150 million people have the chronic form of the disease and as many as half a million die of it each year. If the trial succeeds and the treatment is approved, it will be a big deal.

Exactly how big is difficult to grasp. Graham and his colleagues point to the case of Pharmasset, a Princeton-based company that developed the current hot new hepatitis C treatment, a drug called Sovaldi. Unlike older treatments – courses of antiviral drugs that leave patients with heavy flu-like symptoms and other side effects for as long as a year –

much milder side effects. Pharmasset took the drug to the first stage of human clinical trials in 2011, and at that point the American pharmaceutical giant Gilead snapped them up for $11 billion.

Sovaldi arrived on the American market at the end of 2013, and in the first six months of 2014 Gilead sold almost $6 billion worth. In the US, a course of treatment costs a staggering $84,000. This price, and the requirement for regular daily doses, makes Sovaldi less useful in the developing world, where three quarters of all hepatitis C patients live.

TT-034 aims to achieve results as good with a single injection. For researchers and pharmaceutical companies, it will prove that ddRNAi can work, and point the way to radical new treatments for everything from HIV to cancer to chronic pain. For Graham it will mean vindication, and for Benitec vast amounts of money.

And TT-034 is just the beginning. Benitec has five other ddRNAi-based treatments at various stages of development. In April, the company raised more than $30 million from institutional investors to finish the TT-034 trial and keep other projects ticking along. Only one of these, a lung cancer treatment called Tribetarna, is happening in Australia – the others are carried by collaborators in Europe, the US and China.

Benitec had all but given up any idea of making things, instead simply licensing out its patents and chasing people it suspected of infringing them.

A few weeks after the initial lunch, I was in a wedge-shaped meeting room at the University of NSW's Lowy Cancer Research Centre in Kensington, where Graham and Peter French were checking in with Maria Kavallaris and her team for the latest on Tribetarna.

On a screen was projected a graph that looked like a wonky staircase descending from left to right. Kathleen Kimpton, who had done the lab work, explained for my benefit that it was a Kaplan-Meier survival curve, representing the number of patients (mice, implanted with aggressive lung tumours and treated with Tribetarna) who were still alive at a certain time after treatment. As time went on – three days after treatment, four days – the graph started to step downwards as mice died off, or as Kimpton put it in clinical language

"So we have a few dying – sorry, 'eventing'," he said. "Some mice are eventing early on, and then we still have some alive – *unevented* – at the end. Sorry." He tried not to laugh. "Eventing."

Kimpton looked a little flustered, and French cut in with his suave baritone.

French is a former research scientist himself, and he wanted to check how this trial, which involved multiple treatments, compared with a previous single-treatment trial. Benitec was founded in 1998, but by the time French took over in 2010 it had fallen on hard times. Due to a combination of technical, legal and financial complications it had all but given up any idea of making things, instead simply licensing out its patents and chasing people it suspected of infringing them. French has turned it around.

Tribetarna is a treatment for non-small-cell lung cancer, which is the most common kind of lung cancer and does not respond to normal chemotherapy. The cancer cells contain a gene that produces a protein called class III beta-tubulin (βIII-tubulin), which protects them from chemotherapy drugs. Tribetarna (tri-beta-RNA) aims to "silence" that gene, preventing it from producing βIII-tubulin and rendering the cancer susceptible to normal treatment.

The results of the mice tests were promising, if not quite as good as had been hoped. Testing would continue. Science would grind on. If this treatment ever makes it to humans (years hence, or decades), it will improve the outlook for a lot of people with lung cancer, but it won't be a cure. There are no miracles.

After the meeting, Graham and French debriefed on the drive back to the Benitec office in Balmain. They made an odd couple: both in their mid 50s, French the square-shouldered businessman with contagious enthusiasm, Graham the schlubby genius who sneaks durries in the loading dock. French was sketching out next steps while he drove – checking on the development of tests to determine drug dosages, musing about possible shareholder announcements – while Graham switched with occasionally unnerving speed between precise technical details, idle chitchat and jokes about "eventing".

French took us on a detour through the back streets of Balmain to show me, as he put it wryly, "Benitec's main corporate goal". We got out at Yurulbin, a park at the end of a long spit of land with a spectacular view over the water, which French invited me to appreciate with an expansive, proprietorial wave of the arm.

"We're the biggest biotech company in Balmain," he said.

"Maybe even Rozelle, too," Graham added.

French turned from the view to point at a mansion perched at the top of a steep garden that ran straight down to the water.

"One day I'm going to walk up to that house with a suitcase full of cash, knock on the door and tell them to nick off."

"See that?" he asked. "That was my father's house."

The story, as he told it, is that his father sold the house for next to nothing during World War Two, in a panic to escape the waterfront after the Japanese submarine attacks on Darwin.

"Anyway," French wound up, "that's the goal. To buy back the house. One day I'm going to walk up to that house with a suitcase full of cash, knock on the door and tell them to nick off."

He thought for a moment. "Actually, don't print that." Another pause. "No, it's all right if you do."

Everyone at Benitec thinks they're going to get rich. There's no shame in it; it's just how things work. Eventually, either they will succeed in getting a drug to market (or get it far enough along that a bigger company buys them out) or they will fail. Pharmasset crops up often in conversation, along with the magic figure of $11 billion.

"It's a pretty standard play for a company like Benitec," according to David Blake, a Melbourne-based biotech investment adviser. Blake has published a weekly newsletter,

says, "it's like a tree that wasn't watered for years, and you think it's dead, and then all of a sudden it bursts into flower".

Benitec's offices are rented rooms in the old Big Sister cake factory, a Balmain institution long closed down, its solid brick shell pierced with skylights and glass walls and lined with institutional carpets and plasterboard partitioning. This is the headquarters, at least – much of the time, Graham says, Benitec functions as a "virtual company". Graham works mainly from Brisbane, where he lives with his family, and there are a few staff in the US. Lab space, and expertise in everything from chemical assays to clinical trials, is hired as needed in places from Sydney's suburbs to eastern Europe. The company is a conglomeration of people and money and contracts wrapped around the intangible core of those patents that Graham took out in the late '90s. All that really seems to hold it together is French's drive and the light atop an imaginary hill of cash.

French sees himself as Steve Jobs to Graham's Wozniak. Building Benitec's profile is what he does: at conferences and investor meetings, in as much press as he can manage. He's good at selling the dream: in the year to June 2014, Benitec's share price more than tripled, mainly due to developments in moving TT-034 closer to market.

French joined Benitec in 2009, when, as he likes to say, the company had only one and a half employees. His role as chief scientific officer took it to two and a half people. He doesn't seem to do anything by halves: within a year or so he had become CEO and was bringing the company back to life. In 2009 he also self-published a novel, *Live Your Life, Love, Row*, the plot of which revolves around cryptic crosswords and rowing, both pastimes French enjoys.

He seems not to have stopped moving since. With some glee he relates the story of how, after a frenetic week of round-the-clock investor meetings at a JP Morgan biotech conference in San Francisco the previous January, he found himself in a New York emergency department in the middle of the night due to a combination of exhaustion and food poisoning. First thing in the morning, he checked himself out and went to his next meeting.

Graham was heading to Pharmaxis, a pharmaceutical company based in the northern suburb of Frenchs Forest, where Benitec had another researcher working on Tribetarna. The drive took three quarters of an hour, and Graham likes to talk.

He was born in Wagga Wagga, he told me, and moved around a lot. His father had managed pubs and hotels from Tumbarumba to Ulladulla, and the family had often lived on farms. In 1982, after completing a science degree at ANU, Graham went to the Walter and Eliza Hall Institute (WEHI) in Melbourne for his doctorate, in which he studied the genetic basis of cancers.

The conventional thing to do next would have been to move to the US for an academic position, but Graham's first child had just been born, and he had doubts about academia, and anyway he wanted to stay close to the applied end of science.

In 1987 he was offered a job at a newly formed company called Calgene Pacific, one of the first Australian biotech start-ups. Biotech – broadly speaking, the use of micro-organisms and cellular processes as technologies to be harnessed like any other to industrial production – was the next big thing in those days, as it has been, on and off, for the quarter-century since.

At WEHI he'd seen the excitement around Genentech, the American company that released the first genetically engineered medicines in the 1980s. (Genentech now employs upwards of 10,000 people, and in 2009 was bought by F Hoffman-La Roche AG for almost $50 billion.) Taking the same ideas to plants was going to change the world, Graham thought, and he wanted to be there when it did.

Calgene Pacific was a subsidiary of Calgene, then the second-biggest plant biotech company in the world (since absorbed by the agri-tech behemoth Monsanto). It set up a lab among the red-brick factories and warehouses of the yet-to-be-gentrified inner Melbourne suburb of Collingwood. The company was interested in flowers: things like prolonging the shelf life of cut flowers and modifying the colour of the petals by genetic manipulation. The flagship project was the quest to engineer a blue rose.

Graham's jump from medical research to agriculture was not as large as it may seem. From a molecular biology perspective, cancer-causing viruses and flower pigmentation are not such different subjects. The fundamental questions are the same: How are the genetic patterns of DNA translated into the concrete forms of life? How can we change one by changing the other?

Calgene Pacific's plan to make a blue rose was relatively straightforward:

1. Find a blue flower.
2. Isolate the gene that makes it blue.
3. Splice that gene into the genome of a rose.
4. Profit!

The implementation proved more complex. In 1991, the company made a minor splash with an announcement that it had isolated the gene that made petunias blue. Soon after, it bought a Dutch competitor called Florigene and adopted its name, and by 1995 it had managed a "blue" carnation that was more mauve – knocking out the native red pigments entirely has proven elusive. Demand was weak. (In 2000, Florigene was saved from bankruptcy by Nufarm, an Australian herbicide and pesticide company, and in 2003 it was bought up by the Japanese company Suntory. In 2009, Suntory released the Suntory Blue Rose APPLAUSE™, a pale $30-a-stem creation in what you'd have to call a shade of purple.)

By then, Graham was long gone. Around 1992, he thought, *Hang on a minute – aren't I supposed to be doing real science?* and took himself and his family off to Canberra and CSIRO's plant industry division, where the RNA interference puzzle came into focus.

"I've got a PowerPoint that explains the science of it, that we can go through later," he said. "How I came up with the idea. The intellectual process."

The PowerPoint presentation is the one he delivers to investors who want to understand Benitec's science. You need to be well informed to invest in biotech, to have an idea of a company's prospects. There is a cottage industry of biotech investment advisers like David

spiel Graham delivers is a notch or two more technical than you might expect from a spruiker's slide deck.

The first thing to know is what Graham had called "the central dogma" at our first meeting: DNA makes RNA makes protein.

A DNA molecule, essentially a long chain of smaller molecules called nucleotides, acts as a template to produce an RNA molecule, and the machinery of the cell then reads a sequence of nucleotides in the RNA molecule as instructions to produce a particular protein. Different proteins make up almost everything in the body. (This is a horrendous oversimplification. The inside of any living cell is an entire world.)

A gene is the sequence of DNA that produces a particular protein. In a flower, for instance, the pigment that colours the petals is a protein, and one way to change the colour of the flower would be to manipulate the gene that produces the pigment. If you stop the protein being produced, you have "silenced" the gene.

The way Graham tells it, he was the right man in the right place at the right time. Three pieces of information came together to lead him to his RNA interference discovery. The first was the "antisense" approach to gene silencing, which had grown from the work of the American molecular biologist Paul Zamecnik in the late 1970s and early '80s. This involved injecting cells with a sequence of RNA that was complementary to the RNA sequence produced by the gene you wanted to silence.

The inside of any living cell is an entire world.

The second piece of information was the work of another American, Richard Jorgensen. Graham had read about Jorgensen's attempts to make petunias more purple by injecting them with an extra copy of the gene that produced their purple pigment. Jorgensen found that the petunias became white instead or displayed complex patterns of purple and white. He called this phenomenon "cosuppression", as the two copies of the gene seemed to be suppressing one another.

The third piece of the puzzle was Graham's own work on producing virus-resistant plants

virus, an aphid-spread infection that wipes out 20 million tonnes of potato crop every year around the world. The potato-chip company Smith's partly funded the work. One method was to attempt to make the plant produce a protein that matched a protein on the coat of the virus. This resulted in some resistance to the virus, though – like antisense and cosuppression – no one was really sure why it worked.

Around 1994, Graham came across a paper by the American researchers John Lindbo and William Dougherty that linked viral resistance and cosuppression, and highlighted the role of RNA. "That was the jewel," Graham said. "It fucked my life up."

Graham realised that all three phenomena could be explained if double-stranded RNA were responsible for gene silencing. When a single strand of RNA meets a complementary strand, the two can join together like the two halves of a zipper to form a length of double-stranded RNA. Graham proposed that when a cell encountered double-stranded RNA, it would then destroy any RNA that matched either of the single strands. (In nature, double-stranded RNA occurs only in certain viruses.) He performed some experiments that established this to his own satisfaction, and then tried to get support to pursue the idea further. Though he was working with plants, he was thinking about animals, mammals, humans. "We should be doing this for HIV," he told his CSIRO colleagues.

Support was not forthcoming. "You go too far outside the box, people think you're crazy. And most of the time they're right. I didn't think I was crazy, though."

Frustrated, in 1997 he packed up again, this time to head to Brisbane and the Queensland Department of Primary Industry (QDPI). Graham's university supervisor, Ken Reed, was there, and he knew Graham well enough to take seriously his crackpot double-stranded RNA idea. Graham's other big idea was a method for creating double-stranded RNA to order. The gist is that you make some DNA that codes for a strand of RNA that contains a given sequence (the "target sequence") *and* its complementary sequence. When the DNA is introduced into a cell, it produces the RNA, which will then fold over on itself to create, as Graham called it, a "short hairpin" of RNA that will trigger the cell to attack

Graham's bread-and-butter work at QDPI was attempting to create a transgenic pineapple that would resist blackheart, a common kind of rot. At the same time, he did some proof-of-concept experiments to establish that his short hairpin RNA idea was feasible, and in 1998 he lodged a patent application. "If you want to apply complex tech to the world, the way to do it is commercially. Science is part of it, but you've got to get the bloody money."

The US scientists Andrew Fire and Craig Mello arrived at this same idea about double-stranded RNA via quite different means: they studied the genetics of the roundworm *Caenorhabditis elegans*. In 1998, they published a widely cited paper on their work, and in 2006 they jointly received the Nobel prize for physiology or medicine.

On the road to Pharmaxis, Graham took a few wrong turns, despite the GPS navigation's best efforts. Not long after lodging his patent application in 1998, he told me, he and Ken Reed established Benitec with the encouragement of their employers at QDPI.

Graham soon heard from some angry former colleagues at CSIRO: after his departure, other scientists – led by Peter Waterhouse and Ming-Bo Wang – had pursued his line of research and tried to lodge a patent of their own, only to discover that Graham had got in first. This caused serious friction: they believed Graham's work belonged to CSIRO. Graham disagreed, arguing that progress he had made after leaving CSIRO was the patentable thing. The corporate dispute was eventually resolved – CSIRO took a stake in Benitec and retains ownership of applications in plants, while Benitec has the rights for applications in mammals – but it put an end to Graham's friendship with Waterhouse.

Graham is circumspect about the details ("All the CSIRO stuff needs to be, ah, *messaged*"), but his story is at odds with the official CSIRO version, which barely mentions him. Jan Bingley, CSIRO's general manager for business development, says, "I'm not surprised. To be quite honest, you're probably going to get cagey answers from me, too." Waterhouse did not respond to a request for an interview for this article.

In late 1998, the prestigious *Proceedings of the National Academy of Sciences* published a

In 2007, when the prime minister's prize for science was awarded for the discovery of RNAi it went only to Waterhouse and Wang.

"Well, it's just business," Graham said as the GPS told us we were nearing the business park in Frenchs Forest, and he parked the car a couple of hundred metres ("a cigarette walk") from the Pharmaxis building.

At Pharmaxis we met Josh Moses, the researcher working with Maria Kavallaris and her team. The goal is to develop a test that will eventually be used to calibrate the dose of Tribetarna required to make the lung cancer treatable. There are no off-the-shelf tests for this kind of genetic treatment.

Where a conventional therapy might involve injecting a simple chemical, Tribetarna (like TT-034) is a specially modified virus that inserts custom-made packets of DNA into cancerous cells. Due to the many stages of the process and the complexity of the interactions, there is no simple way to calculate the relationship between the size of a treatment dose and the size of its effect.

This kind of work was all completed long ago for TT-034, and Benitec didn't even need to do the work itself.

Around 2000, Graham and Ken Reed had decided it was time to quit their day jobs at QDPI and get serious about Benitec. RNAi was taking off in labs around the world (*Science* named it 'Breakthrough of the Year' in 2002), and Benitec owned a little piece of it.

They decided to establish a presence in the US – the market was larger, the biotech scene was larger, and at the time there was a shortage of lab space in Brisbane. In 2004, Benitec bought a Silicon Valley–based biotech company already working on a different RNAi treatment for hepatitis C, and set to work. The same year, Graham's patents – Benitec's main asset – were challenged by a rival company, and later overturned.

Though Benitec eventually had the patents reinstated in 2010, things looked grim in 2006 – investors were spooked, money was running out. There was little for Graham to do, so he returned to Brisbane to work on some CSR-funded sugarcane research. Benitec cut its losses and closed the Californian office. Some of its staff, including David Suhy, the scientist running the hepatitis C project that would eventually produce TT-034, spun off a company named Tacere and raised money to continue their work.

In 2008, Tacere started working with the pharmaceutical leviathan Pfizer, who put in three years and "in the neighbourhood of $10 million", according to Peter French, on developing TT-034. In 2011, the research was a minor casualty of a restructure: Pfizer closed a lab, handed the results of its investment back to Tacere and went on its way.

Meanwhile, Peter French had taken the reins at Benitec in June 2010. His first two decisions were simple: buy back Tacere and TT-034, which was by then almost ready for clinical trials, and get Mick Graham back on board.

Since Benitec's purchase of Tacere, the hepatitis C research has taken up most of the company's resources, as it is the closest to clinical trials and hence to a possible payday. If Benitec can get TT-034 approved by the FDA, it will be the first gene therapy commercially available in the US. As the first of an entirely new class of treatments (and an irreversible one that modifies the DNA in the patient's cells), it faces extremely detailed scrutiny. By the same token, if it is approved, then the creation and approval of other ddRNAi treatments will become easier.

Other projects, like Tribetarna, have been moving more slowly. The tests that Moses was developing are a very early step in that process. There were still some imperfections, but Graham didn't appear too concerned. He's done a lot of this kind of testing himself, "but never worried too much about doing it with precision", he said with a breezy big-picture assurance. "We guess the amount of frustration that will happen. What I do is figure out the time it will take and then add 30%."

"Science doesn't always go exactly the way you want it to," Moses added, as we took our leave.

"There's a view in science that the cheapest thing in the world is an idea," Graham said on the drive back to Benitec HQ, "because most of them are wrong."

"Which is not an unreasonable view," he went on. "You come up with something as outlandish as saying, 'See this bloody petunia? I can cure HIV with this' … You say, 'Please give me the two or three hours I need to explain,' and it's very hard to get that."

An idea is cheap, and even one that's right is worth only a little more. To get from Graham's idea at the CSIRO plant labs to where Benitec is now has taken near 20 years, tens of millions of dollars and a lot of luck. And still nothing is guaranteed. If the TT-034 trials fail, it could all be over – and it might not be because Graham's idea is wrong or because ddRNAi doesn't work or is inherently unsafe. Whatever the reason, investors would be unlikely to stay interested.

If the trial works, everything will be different. And not only for Benitec. The door will be open to a whole new world of medical technology. "This came out of CSIRO," Peter French notes. "It really shows how supporting fundamental research can lead to technologies that change the way the world works." With characteristic enthusiasm, French has plans to one day turn Geelong's soon-to-be decommissioned Ford factory into a high-tech drug plant, saving Australian manufacturing in the process.

Graham has less burning zeal for the commercial outcomes, but has no doubts about the science. He's just looking forward to seeing a practical outcome of his long-ago outlandish idea.

Companies come and companies go. Most of them don't last. Graham takes a philosophical view. "Someone will make this work," he says. "It might not be us – I hope it's us – but someone will do it."

MICHAEL LUCY

25 entries

Michael Lucy is a writer based in Melbourne.

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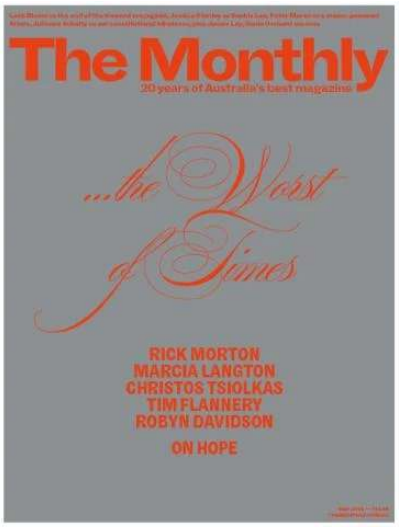

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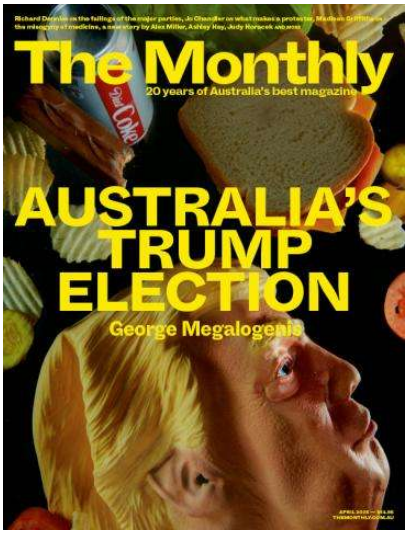

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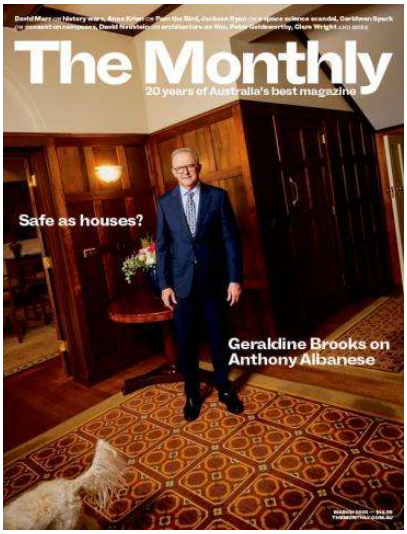

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