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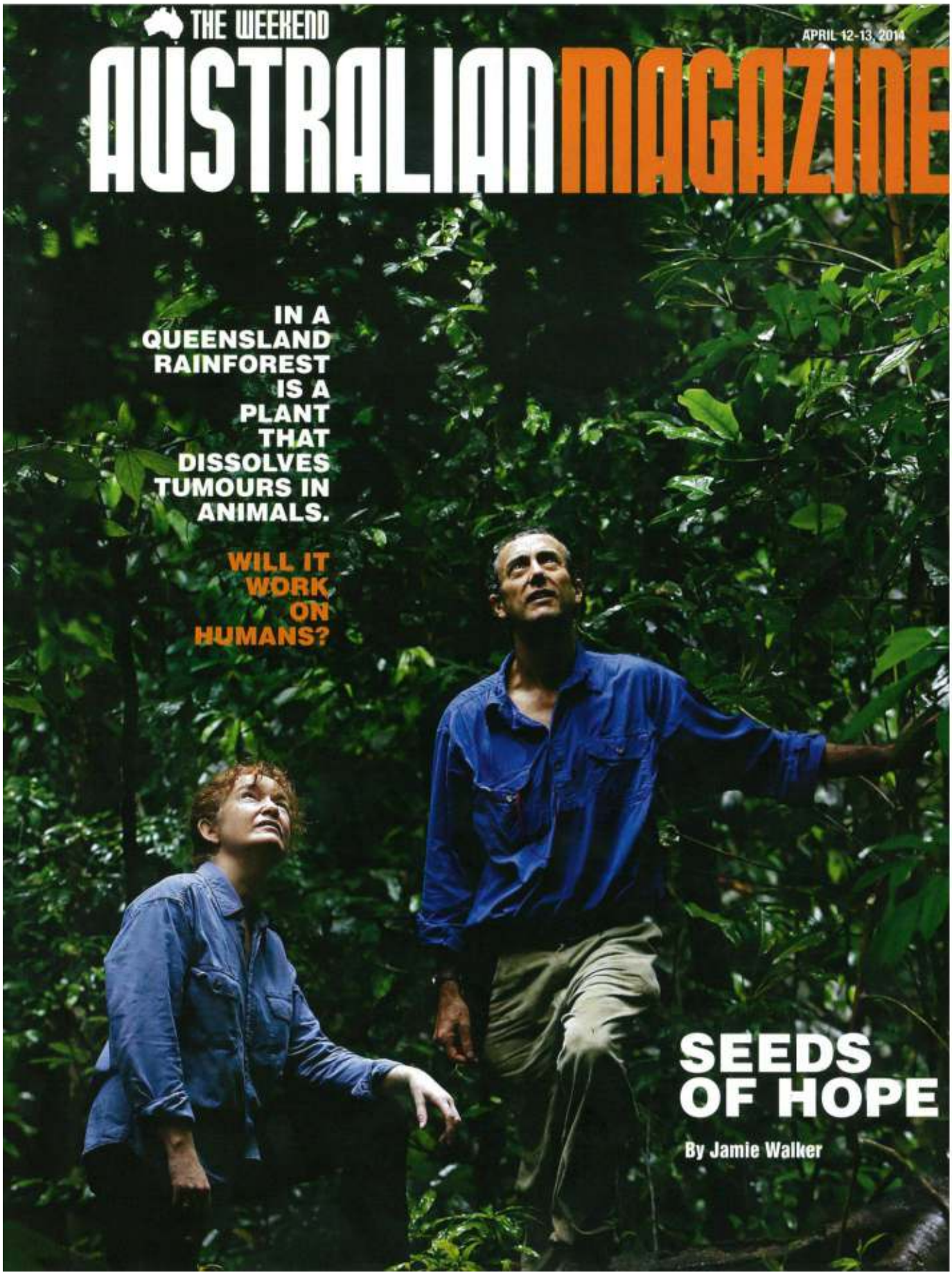
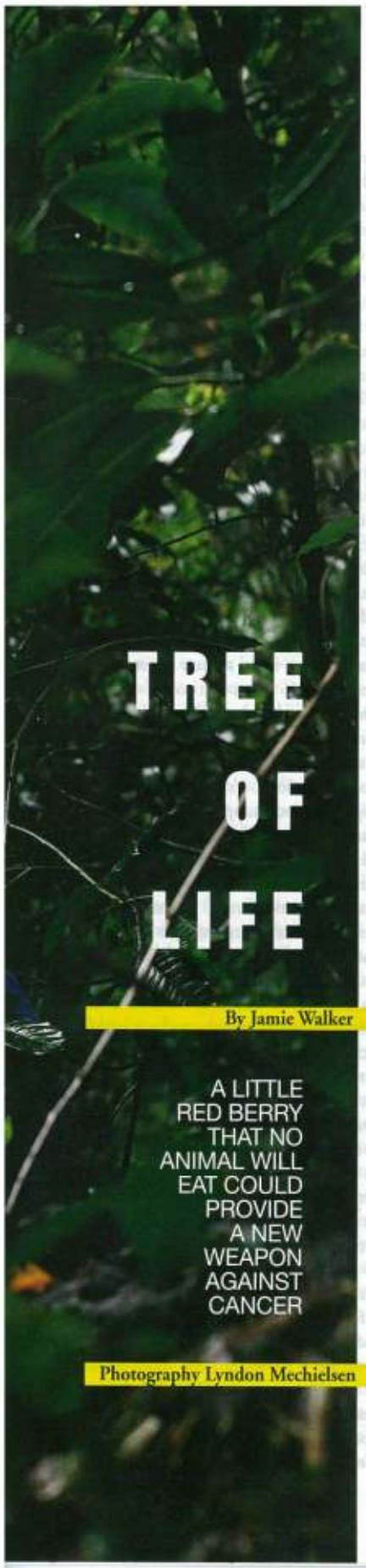


IN A QUEENSLAND RAINFOREST IS A PLANT THAT DISSOLVES TUMOURS IN ANIMALS.

WILL IT WORK ON HUMANS?

SEEDS OF HOPE

By Jamie Walker



TREE OF LIFE

By Jamie Walker

A LITTLE RED BERRY THAT NO ANIMAL WILL EAT COULD PROVIDE A NEW WEAPON AGAINST CANCER

Photography Lyndon Mechielsen

This journey begins in a tangle of emerald foliage, deep in a north Queensland rainforest. Victoria Gordon is crouched by a clearing, slapping at leeches and insects. Like her husband, Paul Reddell, she's as wet as can be. There's no way to keep dry, nowhere to shelter in their line of work. Hour after hour they sit tight while the rain tumbles down in big fat drops and rat kangaroos nose hungrily around the berries lying near their feet. Something doesn't add up. The diminutive marsupials should be feasting on the nutrient-packed seeds of the blushwood tree. It's a jungle out there so why would they pass up an easy meal? Instead, they bite into the kernels and push them away, as if fire to the mouth. The two scientists take careful note. They will watch this pantomime for hours at a time. How intriguing.

Like the song says, from little things, big things grow. Gordon and Reddell are forest ecologists, trained to look past the trees to see the woods. Their specialty is plant defence mechanisms. What's going on beneath the spindly blushwood has got them thinking. The chemical reaction is powerful enough to deter the scavenging animals without killing them. Could there be an application for people? It's just a hunch, but it turns out to be inspired. When they send off a batch of crushed kernels to a commercial lab in Sydney, the results come back with bells on: their powerful anti-cancer properties warrant a closer look. Scientists at the QIMR Berghofer Medical Research Institute in Brisbane test the compound, dubbed EBC-46, on a tumour cell line and are astonished by its effectiveness. When applied to a laboratory mouse implanted with human skin cancer, the melanoma turns red and purple, then melts before their eyes. The year is 2006 and Gordon and Reddell have no time to waste. Up to 100 Australians a day are dying of cancer.

Since then, the drug has been tried experimentally on stricken dogs, cats, horses, pigs, sheep, ferrets, guinea pigs, goanna, birds, even the endangered Tasmanian devil, obliterating tumours in nearly all of them. Animals that at best faced the amputation of a cancerous limb have received new leases of life, their scars barely visible beneath regrown fur. (The drug also triggers a healing process that repairs wounds.)

Now, at last, people look set to be treated. Gordon, Reddell and researchers at QIMR Berghofer have years of scientific research detailing how "a single … injection" of EBC-46 killed most kinds of large-mass tumours and cancerous tissue in 70 per cent of the animals that were monitored. All things being equal, an opening Clinical Phase I trial involving end-stage melanoma patients and those with brutal head and neck cancers will be under way at Australian hospitals by September under a fast-track scheme that allows cancer products to be tested on patients sooner than some other drugs.

"It's time, we need to get this into people," 54-year-old Gordon says in her no-nonsense way. She is deeply invested in EBC-46, as one could easily imagine. It goes beyond the sweat and tears that went into the discovery and development process and, yes, the money she and Reddell, her colleague and life partner, stand to make should they sell their unlisted company or take it public.

Cancer, you see, is an intensely personal matter to Gordon. It killed both of her parents, her paternal and maternal grandparents and her sister, Cheryl, who begged Gordon to toss away the rule book and give her the drug six months before she died last December. "I'm on a timeline," she explains. "There is cancer through my family and that has implications. I have already lost loved ones. I'm sure that more of my family will present with cancer, as my sister did. I wasn't ready for her. So I have some incentive, real incentive, to get this drug through."

Victoria Gordon was a girl of 12, one of seven kids, when Richard Nixon made the "war" on cancer official US government policy in 1971. The then president said if America could put a man on the moon it would beat cancer in five years, neatly in time for the US bicentennial. It never happened, of course; the more we learn about cancer – or, more accurately, the suite of diseases that comprise cancer – the more opaque it seems. Yet four decades and seven presidents on, Barack Obama is still talking up the prospect of curing it in "our time".

Few scientists speak in such absolute terms, Gordon among them. She is cautious when discussing EBC-46's potential at this delicate juncture of the registration process. "We've made a lot of progress but we have a long, long way to go," she says. Peter Parsons of QIMR Berghofer, the veteran medical scientist who first tested it on live cancer cells, points out that the pre-clinical stage is the "valley of death" for new drugs. Most fall over long before reaching the critical and vastly expensive proving exercise of a Clinical Phase III trial, which is dependent on the results of the earlier studies – and cash. Potentially, buckets of cash.

Still, there's a quiet confidence to how they are all going about this laborious business. Gordon and Reddell's company, EcoBiotics, began as a cottage industry clustered around their home in Yungaburra, a rainforest-fringed hamlet on the Atherton Tablelands, 90 minutes' drive west of Cairns. The operation reaches across the world to a pharmaceutical plant in Iowa, which is producing the compound to medicine-grade standard, preclinical R&D in Switzerland, the US and Canada, and equine trials in London.

They met 20 years ago, after Gordon threw in her job with a plantation timber company in Tasmania and moved to north Queensland to work for the CSIRO's Tropical Rainforest Research Centre, where Reddell, 54, was a principal scientist. Her background is in chemistry and microbiology; he's a "bloodhound" of an ecologist who can sniff out just about anything in the rainforest, Gordon says.

The blushwood tree was just one of a number of plants that had attracted their attention. An otherwise unloved specimen, it grows beneath the forest canopy to a height of 15m, too slender to interest loggers, skittish of direct sunlight. But the early results on the seed extract made it their priority. Gordon left the CSIRO to go fulltime on their new venture. The couple sold everything they could part with – a horse float, their bicycles, her jewellery – to set up a laboratory in the garage of their highset home. Gordon focused on the business side, striking a profit-sharing deal with the Queensland government and private landowners for access to local rainforests, the only place in the world where the blushwood tree is known to exist. Reddell, having followed her out the door at CSIRO, immersed himself in the nitty-gritty of producing the active compound and prepping native trees to be cultivated. To date, they have raised $36 million from investors to develop the drug through a subsidiary company, QBiotics.

Yet even now they struggle to explain exactly how it works: as Parsons admits, the mechanism isn't completely understood, though his team at QIMR Berghofer has been poring over it for most of a decade. What's clear is that it attacks cancer in a way not seen before with conventional therapy.

When injected into a tumour or applied by gel – the growth has to be on or erupted through the skin for the purpose of the current studies – the drug activates a local tissue response through an enzyme known as protein kinase C (PKC) or related molecules, precipitating an onslaught that cuts the blood supply to the tumour and kills it. Cancer begins with a short circuit in a single rogue cell that causes it to grow uncontrollably. But the disease can't take hold unless it suppresses the immune response. Blinding the immune system is the sinister secret to cancer's success. EBC-46 blows that cover.

The outcome can be visible to the naked eye within minutes. The flesh-coloured lesion takes on a reddish tinge as its primitive vascular system collapses. Soon, it's a bruised purple, a telltale sign the blood supply has been choked off. Researcher Glen Boyle could hardly believe the speed of the process when he first saw it in one of Parsons' laboratory mice in 2007. (The original recipient, nicknamed Agent 46, became something of a celebrity, living to a ripe age free of melanoma.) Boyle, today the head of the institute's Cancer Drug Mechanism Group, still gets a kick out of watching EBC-46 in action. "By the time you put the mouse back in the cage you can see the swelling … and the tumour is starting to turn blue. Come back in five minutes and it is purple. You come back the day after and it is very purple and a couple of days after that, there is a scab where the tumour used to be."

In 2009, Gordon and Reddell tested it for the first time outside the lab on Bonny the blue cattle dog. Again, there was a personal dimension to this. Bonny was their much-loved pet, aged 18 and ailing with advanced oral melanoma. After injecting the tumour, Gordon was horrified by how rapidly it broke down, the putrid discharge oozing from the dog's mouth "like fat off a barbecue". She thought: *Oh my God, what have I done to Bonny?* "It left a huge wound down his throat as it tracked unseen tumour … it looked awful."

Not that Bonny seemed to mind. By day two

Nature's gift: blushwood berry; opening pages, Victoria Gordon and Paul Reddell

he was jumping around like a playful pup. Such examples of "euphoria" have been observed in many animals after treatment. Gordon thinks it may have something to do with relieving the general burden of cancer, lifting "this great weight off the body's systems". The dog's wound healed within a few weeks and he remained clear of cancer until his death about a year later from an unrelated illness.

Herein lies the elegance of the drug, or at least in how it has been seen to work in animals. In most cases, a set of five or six injections does the trick, but a follow-up course can be required. Evidently, the response to EBC-46 doesn't stop there. It kicks up a gear, healing the wound with soft, new skin. Of the 344 animals treated to date – about two thirds of them dogs – 78 per cent ended up cancer-free or with tumour mass reduced by more than half. Fewer than nine per cent failed to respond. Bone cancers and highly fibrous tumours have proved to be resistant, possibly because not enough EBC-46 can penetrate.

At the Tableland Veterinary Services clinic in Atherton we meet Carmel and Tom Gavin and their bright-eyed shih tzu terrier, Millie. The little dog had had unsuccessful surgery on a mast cell tumour on her left paw the size of a 20¢ piece. "We were looking at amputation or death in the end," Tom says. Millie received a course of EBC-46 on January 7 and the growth dissolved in typically messy fashion until what was left of it dropped onto the floor. Three weeks later, the wound is a healthy pink, nearly healed. "I don't use anything else on mast cell tumours," vet Justine Campbell says of a cancer that accounts for about a quarter of tumours in dogs.

There have been disappointments, however. After years of wrangling with bureaucrats, the drug was finally tried on Tasmanian devils with facial tumour disease, an aggressive cancer that has cut a swath through the wild population, jeopardising the species. "It's a sad story," Gordon admits. Three animals were treated in early 2013 with very light doses, which destroyed most of the growths on them, a highly encouraging result. However, by the time agreement could be reached for a follow-up treatment with the ethics committee overseeing the trial, it was too late for two of the devils. "We really needed to do more work," she says ruefully. Her door is open, however, and the Tasmanians may opt to give it another shot.

For now, use of the drug in animals is confined to cancers of the skin or tumours growing on it – in effect, those a needle or the gel can get to. In the veterinary space alone, that's a lot of potential business. Gordon was in the US in February discussing planned final veterinary clinical and safety studies with the Food and Drug Administration, the world's premier regulator of medicines. The plan is to have a veterinary product on the market within three years. (It's currently available to animals in case studies as a treatment of last resort.)

Brought to heal: Tom Gavin with his shih tzu terrier, Millie

While there can be no guarantee the drug will help people, Gordon can't see why it wouldn't. Researchers are yet to encounter a species of animal that can't be treated. "It gives us a lot of confidence," she says. Parsons, the 71-year-old team leader of QIMR Berghofer's Drug Discovery Group, says the drug should work on most solid cancers – the beauty of activating the PKC-related pathway. The signalling molecule is found in just about every nook and cranny of the human body, so "it doesn't matter whether it is a melanoma or a breast cancer … it could work in most tumour types if local injection is feasible". He, too, is reassured by the results in companion animals. "They are real tumours, they are natural tumours that have come about in the same environment in which people get cancer," he explains. "That's the real deal."

A reality check. Australians are living longer with many cancers as treatments improve: surgery is generally less disfiguring, chemo combinations are more effective and less disabling, therapeutic radiation more tolerable. And there's the new generation of drugs. Formerly a death sentence, chronic myeloid leukemia, for example, can be controlled for years by Gleevec, while the QIMR Berghofer team did much of the heavy lifting to develop the recently approved drug Picato, from the sap of a common weed, to treat sunspots before they turn malignant.

Yet of all diseases, cancer has stubbornly failed to fall to the march of progress by medical science. More people than ever are getting it. This is partly a function of a greying population: the longer you live, the higher the chances that a misfire in your genetic circuitry and exposure to carcinogens will seed a tumour or cancer of the blood or bone marrow. A decline in tobacco use has been offset by Australians' expanding waistlines and love of a drink. In February, the World Health Organisation reported that cancer had surpassed heart disease as the leading cause of death globally. Just on 125,000 Australians will be diagnosed with cancer this year, according to the Cancer Council, a 50 per cent increase on the number a decade ago; there will be more than 44,000 cancer deaths, based on 2011 figures. The direct cost to this country's health system will approach $4 billion.

If cancer is caught early, a patient's chances are better than they have ever been. Nine in 10 women with breast cancer will survive for more than five years. Yet once it spreads, the prognosis for most forms of cancer remains deeply problematic. My paternal grandfather died of pancreatic cancer in 1979, three years after the expiry of Nixon's faux deadline for a cure. His suffering, no doubt, would have been eased by modern palliative care. But his overall prospects were little better than those of a patient today, given the five-year survival rate for pancreatic cancer, a particularly vicious type, is still 5 per cent.

Gordon's sister Cheryl, 61, mother, grand-

mother, professional chef, received the best treatment available in Melbourne after her liver cancer was diagnosed. Targeted doses of chemotherapy were delivered to the tumours, boosting effectiveness and minimising side-effects. To no avail. Cheryl was an early investor in EcoBiotics and knew what compound No. 46 had done in animals. She asked her sister – the only scientist in the family – to give it to her about six months prior to her death on December 14. *What harm could it do? No one need know.*

"I had to say no," Gordon says, the emotion raw in her voice. "It's so important that we tell people … that at this point … we must have particular data before we go further and treat human patients. It is heartbreaking, I know. But there are no shortcuts, not for anyone. The … regulators are there not just as gatekeepers but to protect patients from snakeoil drugs."

Could EBC-46 have helped her sister? Gordon weighs the question carefully. She has thought a lot about this. "[It] may – and I say this strongly – may be able to deal at some stage with liver cancer, but there is no certainty to that. We need to do a lot of work. Personally, I reflected that if we managed to get to the stage where we could treat people, this will be a good drug. I do believe it's a superior drug in the instance of direct [delivery] to the liver than cisplatin," she says of the platinum-containing chemotherapy drug Cheryl received. "I don't have proof of that," Gordon continues. "But I can theorise and say that EBC-46 does certainly have potential in a situation like that. But let me stress, the liver is difficult. That needs to be said because people will read this and start to contact us, and we will have to tell them the same thing: we can't help."

Boyle is equally cautious. He has taken too many pleading calls from those who have run out of options to say anything that would raise expectations of yet another magic bullet for cancer. For all its potential, there is no suggestion that the drug could replace surgery or chemotherapy as a core treatment. For a start, it can't be used systemically, as chemo drugs are, against metastatic cancer. EBC-46 won't "chase down" tumours once they spread, Gordon admits.

Then there's the sticky question of how to manage the sludge that would be left by an internal tumour, assuming it could be broken down. This is one reason why the focus to date has been on surface lesions. Although Gordon is adamant the drug has potential to be used internally, the necessary work is yet to be done. "The sting in the tail is that it has to be put on the outside of the body," explains QIMR Berghofer director and CEO Frank Gannon. "It is highly toxic if it gets into the body unless it can be controlled."

Bearing fruit: Gordon wants human clinical trials to start in September

For now, Boyle believes EBC-46 could come into play after conventional treatment options have been exhausted or for palliative care. He cites the example of an elderly patient who was unable to physically withstand further surgery, chemo or radiation therapy. EBC-46 could provide relief from, say, a tumour impacting on a nerve, improving that person's quality of life. Or it might buy time. "At the moment, that's where I see it … treating things you can't use other methodologies to treat," Boyle says. "But that's not to say where it might be in 10 years' time."

Gordon is pushing as hard as she can to get the human clinical trials under way in early spring. Clinical Phase I is typically a safety exercise to confirm the drug won't harm people, but in oncology studies, patients can also be treated in what is referred to as a Clinical Phase I/II, allowing information to be tapped on its effectiveness. The study will be run through a network of hospitals in different cities with 30 or so patients with advanced melanoma or externally accessible head and neck cancer, "people who need some answers that they are not getting … who really are at the end of the line". Gordon says there is strong interest from medical specialists in head cancer, which is notoriously difficult to treat and often requires disfiguring surgery. Patients can lose a jaw, their nose, slabs of facial bone and tissue. "The head and neck surgeons that we have been talking to for a few years now are basically saying, 'Give us the drug. We're sick of deforming people.'"

If EBC-46 gets through to Clinical Phase III, the critical proving trial that generally involves thousands of patients around the world, it will have burned through all the cash Gordon and her husband have raised, and more. The majority of their 1200 shareholders are mums and dads who have kicked in as little as $1500; the biggest single outside stake in the unlisted company is $1 million. This is more by accident than design. Gordon initially did the rounds of venture finance providers but was rebuffed; prove it up and come back to us, the money-men told her.

The expense of getting a drug to market is staggering, which helps explain why so few get through in Australia. Picato, a rare success story, had $130 million ploughed into it by Danish outfit LEO Pharma before being registered by the Therapeutic Goods Administration last year. In a small pond, Australia's CSL is the nearest thing there is to a big local fish. Yet to meet the development cost it had to license the international rights of Gardasil – the revolutionary cervical cancer vaccine pioneered by 2006 Australian of the Year Ian Frazer – to US group Merck. Gordon estimates that EBC-46 will require north of $600 million to be made into medicine – completely out of their league. She and Reddell have structured the company so that the subsidiary, QBiotics, contains the intellectual property and could be peeled off for outright sale or a stockmarket float.

Are they getting ahead of themselves? They need good corporate planning and execution, quality control, the best people, and, let's face it, a measure of luck to take the next step on what's already been a long and testing journey. Without a trace of smugness, Gordon says: "We're about solving major health problems and in the process conserving the rainforest. It's not a bad combination … I think I'm on a winner when I get up to sell this company, I've got to say."

So here we are, back in the forest, among the blushwood trees and the ripening berries atop them. Reddell has a team of helpers harvesting the crimson orbs. Shaken loose, they fall to earth like oversized gumdrops. Reddell says it's no use trawling the forest, hoping to stumble across another aspirin or penicillin, without knowing what to look for. "We go out with a strategy when we are collecting," he says. "We look at different features of how plants interact with animals, and how they all interact with the environment."

Reddell is cross-breeding blushwood trees to improve their yield, raising them in rows of vineyard-like trellises on a windswept prototype plantation east of Yungaburra. Like opium, another gift from nature when used as a painkiller, EBC-46 can't be synthesised. If all goes to plan, royalties will flow to the Queensland government and private landowners under the agreement covering the couple's discoveries.

EBC-46 is not all there is in the works. They have done deals with a German cosmetics ingredient supplier and a US conglomerate to develop a range of antioxidants, anti-inflammatories, antimicrobial products and – of all things – a skin-whitening cream. Another compound, EBC-23, shows promising activity against prostate and breast cancers; WH-1 is a potential healing treatment for acute and chronic wounds such as pressure sores and tropical ulcers. "It's a great laboratory out here," Reddell says, running a hand through his soaking hair.

Gordon is counting down to the start of the human clinical trials for EBC-46. One of the treated horses has racked up 564 days in the clear; some of the dogs have gone even longer with no trace of a tumour. If these results can be translated to people, it could add up to years of precious life – time she wished she could have had with her sister; time others in the family, herself included, may one day need. "We have never used the word cure," she says. "But the fact is, all those animals are cancer-free."

For all our sakes, let's wish them well. ●

New drugs turn the tables on cancer

From his fifth-floor eyrie, Frank Gannon commands a bird's-eye view of the Brisbane skyline – and of cancer research in Australia. The QIMR Berghofer boss says Australians are mostly living longer with a disease that was once considered a death sentence. The fatality rate has fallen more than 16 per cent over the past 30 years, reflecting advances in detection, diagnosis, surgery, chemotherapy and radiation therapy. New-generation drugs born of medical science's growing knowledge of the genome and biology of cancer are improving the odds. The great hope of unleashing the body's defences against tumours and blood cancers is being realised. "We are at the start of a real revolution in immunotherapy," says Gannon. A snapshot of the advances being made by Australian cancer researchers:

PICATO The gel for treating cancer-causing sunspots was developed from the common radium weed Euphorbia peplus and, like EBC-46, its active ingredient works on protein kinase C to activate the immune system. The gel has been approved in Australia and the US, and can alleviate the need for surgery to remove sunspots, a precursor to squamous cell carcinoma, the second-most common form of skin cancer. Some of the scientists who worked on EBC-46 were involved in developing Picato with Peplin Biotech, the company founded by former CSIRO researcher Jim Aylward.

CSL362 A new entry to the hot field of monoclonal antibody therapy, this experimental drug is in a Clinical Phase I trial for the treatment of acute myeloid leukaemia, one of more intractable types of blood and marrow cancer. CSL is hoping to replicate the success of its breakthrough cervical cancer vaccine Gardasil, after signing a licensing deal with a Johnson & Johnson subsidiary. However, it underlines how the crushing expense of bringing new medicines to market generally dwarfs the resources available in Australia.

ABT-199 One of a new class of anti-cancer agents called BH3-mimetics, the treatment is being trialled for leukaemia and other cancers. It is designed to block the function of the protein BCL-2, discovered by researchers from Melbourne's Walter and Eliza Hall Institute 25 years ago. The treatment achieved outstanding results in a phase I trial of 67 Melbourne patients, clearing cancer in 23 per cent of them and achieving partial remission in a further 61 per cent.

GST Not the tax, but so-called gene silencing technology being developed by listed company Benitec Biopharma. The work dovetails with intensive research abroad. Known more formally as DNA directed RNA interference, the process was developed by former CSIRO scientist Mick Graham to switch off genes that cause disease. According to the company, it has the potential to provide a "single shot" cure for lung cancer, hepatitis strains B and C, and HIV-AIDS. The US Food and Drug Administration recently gave Benitec the nod to commence clinical trials on the hepatitis C treatment.

EphA3 This is a protein identified as a new target for treating the aggressive brain cancer glioblastoma multiforme (GBM). Discovered in leukaemia cells by Queensland scientist Andrew Boyd, EphA3 is also required for a high proportion of GBM to grow and form tumours. It can be targeted by an experimental drug for leukaemia, establishing a fast track for a clinical trial in GBM application at QIMR Berghofer. The protein's presence in GBM may explain why the cancer usually recurs despite chemotherapy or radiation. Despite the best efforts of doctors and medical scientists, survival rates for GBM have barely changed in half a century.