THE AUSTRALIAN

New cancer therapy brings hope

Battling blood cancer in my 20s, I put my faith in a clinical trial for a promising new treatment. But does it actually work?

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From **The Weekend Australian Magazine** June 5, 2021
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Lunch is a hot chook. Breakfast was the remainder of last night's seafood curry, followed by two biscuits and Vegemite toast. A few weeks after starting chemo I am juggling nausea, insomnia and an out-of-this-world - appetite from the prescribed dose of steroids. It is February in Perth. Today, the sun-scorched city is grappling with a Covid lockdown on top of bushfires to the northeast. I'm on the balcony of an eighth-floor unit, one of several within the complex provided to regional cancer patients and carers. Thick smoke clouds loiter above the abandoned streets, and all the while I'm thinking of the pie sitting in the freezer.

We learnt of the relapse about two months ago. It hit like a Southern Ocean storm. I was at my house in Esperance, the beach-blessed town about 700km southeast of Perth, standing half-naked in the bathroom preparing for work on a Wednesday morning. Then I saw it: another lump. It was small, no bigger than a 10-cent piece, and right in the middle of my chest. The same spot as last time. Fretting, I phoned my girlfriend Emily and then the doctor. By the afternoon, a local GP had referred me to Perth for an urgent biopsy.

We were back in Esperance when the results came. Instead of celebrating the end of Term Four at the staff Christmas party, we were in the living room, laptop open, nervously awaiting the haematologist's video call. The six months of remission had been glorious: teaching, health, family and friends, cricket. Now we were hearing confirmation that, after finishing chemo in May, I'd already relapsed with a rare and aggressive form of non-Hodgkin's lymphoma (primary mediastinal B-cell, a subtype of diffuse large B-cell lymphoma).

The doctor spoke earnestly, but all I could muster in response were vacant nods and a virtual thousand-yard stare. He outlined some treatment options. I could try radiation, but he warned this may be risky because of the lump's proximity to the heart and lungs. "Another option is to join a clinical trial," he said, "and try to access something called CAR-T therapy."

He then explained, in simple terms, how a new treatment was making waves in the world of blood cancer. It involved removing T cells – a type of white blood cell central to the immune system – from the blood and modifying them in a lab so that, once returned to the patient, they were "retrained" to recognise and destroy cancerous cells. It was *New Age Blood Cancer Treatment for Dummies*, but this much I could follow. I was at once terrified and intrigued, partly because I didn't like the sound of radiation-induced organ damage in my late 20s. I let his words sink in for a few seconds, then said: "OK, but does it actually work?"

Conventional treatment had failed Bill Ludwig.In 2010, the former US corrections officer, then in his 60s, was dying from leukaemia. His last hope was to join a clinical trial for CAR-T therapy – a new "immunotherapy" being pioneered at the University of Pennsylvania. One of the lead researchers was Dr Carl June, who - several years later would be named by *Time* as one of the world's most influential people.

Doctors took a sample of T cells from Ludwig's blood. In a lab, they were re-engineered with a protein known as a "chimeric antigen receptor" (CAR), so they could then identify and eliminate cancer cells. Before long, the new CAR-T cells were returned to his body. A few weeks later, something remarkable happened: scans detected no trace of leukaemia. Medical professionals, and even Ludwig himself, were stunned. "Did I ever think it would be successful? Not in a million years," Ludwig told *The Philadelphia Inquirer* in 2015. He would live for another decade before dying in January this year from Covid-19.

For Associate Professor Dominic Wall, of Melbourne's Peter MacCallum Cancer Centre, Ludwig's remarkable recovery signified a game-changing moment. "Scientifically, his story was the one that excited me," he says now. "It was the first time I'd seen this magnitude of effect in an otherwise pretty well untreatable disease, at that stage. He was completely out of options, basically preparing for palliative care." In layman's terms, Wall describes CAR-T as a "cancer serial killer": "They're a living drug. When they're reintroduced to you, they live and persist, and they're able to proliferate when they see that tumour antigen and eliminate it... they kill one after another."

In December 2018, a CAR-T therapy known as Kymriah – developed by pharmaceutical company Novartis – received approval from Australia's Therapeutic Goods Administration (TGA). It is now publicly funded to treat Australian patients aged up to 25 with relapsed acute lymphoblastic leukaemia, as well as adults with certain types of relapsed lymphoma, including diffuse large B-cell lymphoma (DLBCL) – the most common type of non-Hodgkin's lymphoma. As of May this year, 186 Australians have received Kymriah across clinical trials and commercially available therapy. (Another CAR-T product, Yescarta, has received TGA approval but is yet to be government subsidised.)

The TGA approvals for Kymriah came on the back of two global clinical trials. The results from the trial for acute lymphoblastic leukaemia (ALL) were most striking: of the 79 "evaluable patients", 83 per cent achieved complete response within three months; the relapse-free survival rate after 24 months was 62 per cent. For the DLBCL trial, the complete response rate after 14 months was 40 per cent, with 12 per cent showing a partial response to treatment. However, many of its participants had a "poor prognosis" at the time of enrolment. "These patients with DLBCL had been through multiple rounds of chemotherapy and many had unsuccessful stem cell transplants, leaving them with few options," said Stephen Schuster, the study's principal investigator. In Australia, Wall says the "real world" results have largely - mirrored those of the trials. "The other thing that is very pleasing to see is a general sense that the [treatment] responses are durable," he says.

As of earlier this year, production of Kymriah has been ramping up domestically. Wall is also chief scientific officer of Cell Therapies, the Australian company that has approval to manufacture the Novartis treatment within the Peter MacCallum Cancer Centre. Previously, even though the TGA had approved the treatment, the T cells of eligible Australian patients were being sent overseas for CAR-T

"programming" at existing Novartis facilities – a lengthy and riskier process, particularly in the midst of a pandemic. "We are in this incredible place where we have sovereign [Kymriah] manufacturing in Australia, which is not the case in most of the world," he says.

It was mid-March at Fiona Stanley Hospitalin Perth, and a squadron of doctors and nurses had gathered by my bed. Some were methodically checking clipboards, the rest watched on silently. It felt like a scene from *ER*. Emily was waiting patiently outside the room with my parents and youngest brother, who'd flown over from Queensland. Minutes earlier, the new CAR-T cells had been returned to my body through a central line – an unnervingly long tube inserted in my neck.

I had agreed to join the trial in early January, following several restless nights and lengthy family discussions while visiting my home town of Toowoomba over Christmas. We saw it as an opportunity to access some innovative, albeit daunting, treatment. The international study in which I'm now enrolled aims to compare the effectiveness of Kymriah against the disease's current "standard of care" treatment – in this case, a stem cell transplant – following unsuccessful frontline chemotherapy. Results from the trial (Australian recruitment has now closed) could prove pivotal in deciding whether broader approvals are given for Kymriah. After six weeks of pre-conditioning chemo, which left me with the nausea and immense hunger, the CAR-T infusion came and went in a flash. Still, the ward was now on edge as we waited to see how my body handled the new cells.

One of the most daunting aspects of CAR-T therapy is the potential side-effects. I'm told of Cytokine Release Syndrome (CRS), an inflammatory response that can result in low blood pressure, sweats, fatigue and temperatures caused by the rapid release of cytokines – "signalling" molecules that aid the immune system – into the blood. In more serious cases, patients can be admitted to intensive care and, in rare instances, it can be fatal. Another hallmark side-effect is a form of neurotoxicity that can cause confusion, hallucination and, in severe cases, seizures. Close monitoring and early intervention are pivotal, so it was no surprise I was watched like a hawk during my week as a Fiona Stanley inpatient, with nurses checking my temperature and blood pressure every four hours.

A few things cheaper than a single CAR-Ttreatment: 12 years of private schooling; a comfortable home in Esperance; a Ferrari. CAR-T is as expensive as it is complex: the therapy costs north of $500,000 per patient. It is classified as a "High

Cost, Highly Specialised Therapy" (HST) under the 2020-2025 National Health Reform Agreement. "This is the peak of personalised medicine," says Wall. "It is expensive to make and administer." For each approved Kymriah CAR-T treatment, the full cost is split between the federal and respective state governments. However, the only states currently delivering HSTs are NSW, Queensland and Victoria; I was able to access Kymriah in Perth through the Novartis-sponsored clinical trial.

Every year, more than 17,000 Australians are diagnosed with a form of blood cancer, such as leukaemia, lymphoma and myeloma – combined, they amount to the second most commonly diagnosed cancer in 2020. More than 5500 Australians are expected to die from blood cancer this year. Leukaemia Foundation chief executive Chris Tanti says further research and investment in treatments such as CAR-T therapy are crucial to combating one of the nation's biggest killers. "We have seen strong, positive strides forward in this space in recent years. As a country, we can't stand still." Tanti says that, while not a "silver bullet solution", CAR-T has "generated enormous excitement" in the medical world. "The lived experience of many Australian blood cancer patients with CAR-T therapy is so far proving positive."

Which leads to the question: could it be effective in treating other cancers? An article published last year in the peer-reviewed oncology journal *Cancers* explored the clinical outcomes of global CAR-T trials for solid tumours such as pancreatic and ovarian cancer. While it found that only 52 of the 375 total patients responded to the treatment, it also concluded that CAR-T presented opportunities in treating solid cancers. Wall says there's "tremendous inventiveness" happening in this space: "We want to see the [positive] results in aggressive lymphoma and acute lymphoblastic leukaemia also available to patients with gastric cancer, lung cancer, renal cancer..."

One sunny afternoon in April, the doctor provides some heady news: four months after the relapse was confirmed, and about a month after receiving the CAR-T cells, scans have shown a reduction in the "size and intensity" of my chest mass. What's more, I'm starting to feel well again: light exercise, sleeping soundly and no longer eating like a labrador. While undoubtedly challenging, the trial has so far proven less toxic on my body than the six rounds of chemo in 2020. I've also escaped any side-effects and, unlike last year, my hair has clung on. The picture, though, should be much clearer after my next PET scan in July. For now, the doctor says with a grin, we're free once again to return to Esperance.

Now, a few days later, we're on the freeway southbound. Gazing out the passenger window through an endless red sea of tail-lights, I can still see the Perth unit complex that we and numerous other regional blood cancer patients and their - carers have for so many months called home. It has been a godsend – and thanks to medical research, we will hopefully never set foot in it again.