How NSW Health's culture of innovation led to a brain tumour breakthrough

Of all the diagnoses that send a shiver down a parent's spine, DIPG (diffuse intrinsic pontine glioma) ranks with the very worst. An aggressive brain tumour, it takes out functions such as the ability to swallow and blink one by one, while leaving the child cognitively intact.

Until now, the only treatment has been radiation therapy, which holds the disease at bay for a few short months. What makes it so intractable is its location in the brain stem, an area so sensitive that until recently, even biopsies were out of the question. All clinicians can do is watch it grow and spread via MRI.

It occurred to neuro-oncology researcher, Associate Professor David Ziegler, that if he could culture some DIPG cells, it would open a door to finding a cure.

But turning a bright idea into actual research turned out to be harder than he thought.

Associate Professor David Ziegler

The medical exceptions

Ziegler has a huge title: he's Group Leader of the Brain Tumour Group at the Children's Cancer Institute, and Chair of Clinical Trials for the Zero Childhood Cancer personalised medicine program, co-led by Children's Cancer Institute and Sydney Children's Hospital, Randwick (SCH). He also holds a conjoint appointment with UNSW in the Faculty of Medicine, is head of the neuro-oncology program at Sydney Children's Hospital, and runs the clinical trials program at the Kids Cancer Centre.

When he first set foot in paediatrics, back in his residency, he thought it would be gloomy and depressing. What he found instead was a mostly bright, happy place. "There were kids playing, there was music, there was laughter," he says.

Paediatric oncologists were also a cheery bunch, thanks to the pace of medical advances. In the 1950s, for example, leukaemia was a death sentence. Today, more than 85% of children diagnosed with leukaemia are cured, says Ziegler. "It's one of the great success stories of medicine."

But brain tumours are an exception. They are now the single disease responsible

for the most deaths in childhood, says Ziegler. And the worst of all brain tumours is DIPG, he adds, because there's no treatment, and no cure. This can be attributed in part to there being an absence of tumour tissue to study. The location of DIPG tumours ruled out biopsies on living patients, while it was thought that tumours collected after death would not generate live cells that could be used in research. As a result nobody, anywhere, was studying the disease.

Eight years ago, Ziegler decided to set up a program so that parents could donate their child's tumour, post mortem. "We'd just had all this fancy equipment delivered to the lab that can screen thousands of drugs," he explains, so he thought it would be fruitful to grow the cells and then see if the machines identified any promising drugs that might target them.

It was a great idea. The cells, extracted from a supposedly dead tumour, began to grow – the first time such a thing had been attempted in Australia. Next, Ziegler's lab developed mouse models that mimic exactly what happens in kids, says Ziegler. "We ended up screening over 4000 different drugs."

A few showed promise. One was derived from the Feverfew plant, which contains a natural compound called parthenolide. "We ended up working with a company making a synthetic form, which we're developing as a new anti-cancer drug."

There was also an anti-malarial drug. "We are about to open our world-first clinical trial of this drug, in collaboration with the leading cancer centres in America, through what's called COG – the Children's Oncology Group," says Ziegler. It will be the first time that an international COG trial of a new drug has been led from Australia.

The discoveries kept rolling in. Another is that DIPG is driven by polyamines, or compounds containing multiple amino groups. "We're working with a company that's made a completely new drug that blocks the polyamines getting taken up into the cells," he says. "It's the most effective drug treatment that anyone has studied in DIPG laboratory models, anywhere in the world."

Some of these drugs are already being tested on patients. Today, Ziegler has a presentation with 'before and after' slides. The first shows a brain scan dominated by an enormous tumour. In the second, the tumour is barely visible. "We've never seen this before," he says.

When it's just the science being discussed, the entire process sounds easy. But it wasn't, because discovery isn't simply a matter of science.

The roadblocks

When Ziegler began, every single grant application was rejected. Nobody believed that dead tissue could produce live cells. Grants administrators were horrified that recently bereaved parents would be asked to donate tissue. Not only that, but as autopsies aren't done when the cause of death is known, there was no path to recovering tissue. Even nurses pushed back, protesting that dying children should not be used for what seemed like wildly experimental trials.

It was the bereaved parents who came to the rescue because they wanted to do whatever it took to save other parents from their experience. Some even delayed their children's funerals, so an autopsy could take place. A group raised $20,000 to get things started – and they also helped secure the ethics approval. A few small grants were then approved here and there. "I used bits of money," says Ziegler; $20,000 here, $50,000 there. "I just put together whatever would get things up and running."

One issue with taking money from private donors is they get to specify how the money is used, when they may not fully understand the process. One group, for example, specified they wanted the money to go to research based on how tumours look under the microscope. "We worked it out by sitting down together," says Ziegler, who explained that the research needed to focus on genetics, not histology (the microscopic anatomy of biological tissues).

Once promising drugs were found, Ziegler had to convince pharmaceutical companies to send them. "Just providing the drug can cost them millions of dollars, and you need to convince them it's worth spending their time and energy on a rare disease."

Finding patients to trial them on isn't the problem, says Ziegler. "The sad thing is that patients are emailing me almost every day from around the world." But this means running a trial across multiple hospitals, and even across multiple countries.

The key to solving cancer, it turns out, is as much about social skills as it is about clinical skills, because there are so many people who need persuading. It's the ability to collaborate and communicate that will raise funds, access drugs, and create international trials. Ziegler adds that being "young and naïve" also helps.

Ziegler says he wishes he could make people realise how devastating these diseases are, and how deserving of investment. With enough money, he says, "we really can find those needles in the haystack and the magic bullets" and send diseases like DIPG packing – just as researchers did with leukaemia.

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