Clone your tumour to fight your cancer

Every tumour is unique – could armies of cancer-infested mice avatars help find the best drugs for each individual?

If you had cancer, would you want to make clones of your tumour? *(Image: Tom Haugmat)*

"The first doctor I saw told me I had six months to live," says Antonia Crawford. She was diagnosed with advanced pancreatic cancer in August 2013, at the age of 43.

She went on to have the standard treatments but, aware that they might not be the most effective against her particular cancer, Crawford also did something quite extraordinary: she had bits of her tumour implanted into a group of mice. Once the tumours had grown in them, the mice were given a range of different treatments, in an effort to find the drug combination that would work best for her. "As a patient, I just didn't have the time, nor could my body have gone through trying all these different drugs on myself," Crawford says.

It's too early to say whether this particular method improves individuals' chances of survival. But there is a lot of interest in the idea. Many groups are working on the somewhat grotesque challenge of growing three-dimensional copies of people's tumours outside the body – essentially, cloning cancers. Simply put, the idea is that if you want to know your enemy, you need to grow your enemy.

While cancer cells have long been grown outside the body, it isn't as easy as you might think. Some, such as [the famous HeLa strain of cells](#) long used in research, thrive outside the body, but most cancer cells die if they are stuck in a dish. And even when they do survive, there is a big difference between a bunch of cancer cells growing in some fluid in a dish and a tumour growing in someone's body.

Solid tumours are a bit like organs: they have a mix of cell types growing in a three-dimensional structure and fed by a dedicated blood supply. "How cells behave in 2D in a plastic tissue culture flask is just not that relevant to what happens in the body," says [Frances Balkwill](#) of Barts Cancer Institute in London.

Balkwill's team and others around the world [are trying to grow realistic tumours outside the body](#) using tissue engineering, but this approach is still at an early stage. The tried and tested way of growing tumours in 3D is to implant bits in mice with an immune system altered so as not to attack human cells. Such xenografts have been used for drug testing since the 1980s.

Now [Champions Oncology](#) – the company that Crawford turned to – is selling this service directly to individuals with cancer. "Cancer is a unique disease, and it is very difficult to work out why some drugs will work for one patient but won't work for another; we need a more rational way to figure out what patients should and shouldn't try," says Ronnie Morris, the company's president.

Beating the Big C

This everyone agrees on. Cancers are already classified into hundreds of different types

depending on which tissue they originate in and what they look like under a microscope. But really there are many millions of kinds. Cancers typically have hundreds of mutations, along with [even more epigenetic changes](). Every tumour is unique – and constantly changing and evolving.

Getting personal

So the more closely treatment can be tailored to a person's particular cancer, the more effective it is likely to be. And personalised treatments are starting to become a reality. People whose tumours produce too much of a protein called Her2, for instance, are given specific drugs that work against this form of cancer. [Genetic tests are also increasingly used]() to identify mutations known to affect how cancers behave. But while the field is advancing extremely rapidly, we are still far from the point where we can predict the best possible drug combination from genetic tests alone.

Indeed, there are reasons to doubt we ever will reach this point. The cells tested might not be representative of the whole tumour, for instance. What's more, the non-malignant cells in a tumour can have a big effect on the way it evolves and responds to treatment.

This, Morris says, is where Champions can help. "Building a very close replica of their tumour that's alive and continues to grow in a host environment gives patients the ability to simultaneously test four or five drugs or combinations, so that they can see which is the most effective."

In late 2013, Crawford underwent chemotherapy and radiotherapy that shrank her tumour enough for surgeons to try and remove it from her pancreas. Her brother paid for a piece of the tumour to be cut up and [implanted on the backs of several mice](). After the tumours had grown somewhat, they were used to "infect" even more mice. Around five months on, Champions had created a small army of what cancer researchers call mouse "avatars". These were given combinations of drugs that genetic testing suggested might work to see which, if any, could shrink the tumours.

Champions says that the animals' suffering is minimal because the tumours grow just under the skin and don't invade organs. This was an important consideration for Crawford. "I know that animal testing is a sensitive subject, but when you find yourself in a position where you're reliant on it, you realise that it's quite vital," she says. "The only other option for me was to go through it all myself; I would be suffering pain, and my time might run out."

The process isn't cheap. Just creating the mouse avatars costs around £1500, and it doesn't always work on the first attempt; the success rate is around 70 per cent, Morris says. Then it's a further £2500 for each drug tested. Given that most patients opt to test four or five drugs, that's £11,500 to £14,000. Is it worth it?

Preliminary studies by Champions suggest that the mice's response to the cancer drugs does reflect what happens in the patient fairly well. In one study, 65 mouse avatars were given the same second- or third-line drugs as the people whose tumours they had received. According to [a poster presentation]() given at a European Society of Medical Oncology meeting last year, there was an 87 per cent correlation between positive responses in mice and humans. "To put that in context, when a patient takes a second- or third-line drug, the chance of success is usually 10 to 15 per cent," says Morris.

Mouse avatars

The numbers may sound impressive, but this was a small study and the mouse avatars were not actually used to choose treatments. Other researchers would like to see more extensive testing of the approach before more people are persuaded to part with their cash.

"Using avatar mice to try to predict patients' responses to treatment is an intriguing new approach to personalising medicine, but it's still at an experimental stage," says Emma Smith of Cancer Research UK. "It may be of benefit to some cancer patients in the future, but we'll need more research to determine if and for whom it might be helpful. In the meantime, it's vital that patients speak to their oncologist before deciding to pursue any experimental testing method."

Even those working in this field are cautious. Matthew Goetz at the Mayo Clinic in Rochester, Minnesota, who is investigating whether mouse avatars can help predict how women with breast cancer will respond to treatment, recalls what happened in the 1980s. "There were companies who claimed that they could figure out the right drugs for your ovarian cancer by growing the cancer cells in vitro and then looking at a potpourri of different drugs," he says. "Those studies were never really borne out or shown to be clinically useful, so I think we need to learn from that. We need to ask: 'What does this mean in the context of standard clinical practice?'."

Goetz, though, is optimistic about the long-term prospects for such patient-specific mouse avatars. One of the most useful applications could be for studying how resistance to cancer drugs evolves, both to identify the best treatments for individuals and to develop better treatments more generally. "A fundamental problem in the clinic is resistance to standard chemotherapy," he says. "If we can grow these tumours that are still viable after being bathed in 20 weeks of standard chemotherapy, and identify drugs that are active in them, I think the chances of those drugs then being successful in the clinic are much better."

But mouse avatars are far from perfect. A tumour growing under the skin of an immunodeficient mouse isn't the same as a tumour growing inside an organ under constant attack from a healthy immune system. The non-malignant cells in tumour xenografts also gradually become replaced with mouse cells. And with personalised treatments, one of the biggest problems is time. Someone with advanced cancer needs pointers to the best drugs for their tumour within weeks; in six months, they might be dead.

However, there may be a shortcut that also better reflects how malignant and non-malignant cells with a tumour interact. In recent years, tissue engineers have successfully constructed an array of complex tissues and organs, including bladders and windpipes. Now cancer biologists are using the same principles to reconstruct tumours and miniature models of the human tissues they colonise, from scratch.

At the Queensland University of Technology in Brisbane, Australia, they do this by first creating a polymer scaffold on which normal human cells are grown. At the same time, cancer cells are grown in a gel-like matrix to create a "spheroid" of tumour cells. Then the two are put together and implanted into a mouse.

This process is much faster than growing chunks of a patient's tumour on a mouse's back, as Champions does. "Even the biggest spheroids we have in the lab take just two weeks to grow," says Daniela Loessner, who is leading the work. "It means we can have established tumours in

mice within one month."

In theory at least, this approach is more likely to reflect how a tumour in a person would behave in response to drugs. It can even be used to study how cancer spreads, or metastasises. For instance, Loessner's team has been studying how ovarian cancer spreads to a tissue called the peritoneum by implanting a scaffold seeded with peritoneal cells and a spheroid of ovarian-cancer cells into a mouse.

"Metastases are often resistant to many of the standard cancer drugs, and this could enable us to test different drug combinations against them and find the ones that will benefit patients," Loessner says. They are not yet using this method to predict individuals' responses to drugs, but this is the ultimate goal of the group.

Another approach is to avoid the use of animals entirely, and grow tumours in a Petri dish instead. This would not only avoid the "yuck factor" of transferring someone's cancer to a batch of animals, but could also have other benefits for cancer patients seeking more personalised therapies. "In vitro would be cheaper, it would be more controllable, it would be faster," says Marilena Loizidou at University College London.

In an incubator in Loizidou's lab, tiny pink jelly beans of colorectal cancer are growing, barely visible to the naked eye. Like Loessner's engineered tumours, these blobs have been built by growing scaffolds of healthy human cells and cancer cells separately, and then combining them. Although the ability to grow cancer cells in 3D gels has been around for some time, incorporating healthy cells as well is very new, Loizidou says. "A lot of the behaviour of cancer and its responses to drugs has to do with the crosstalk between the cancer cells and the surrounding cells," she says. Indeed, the healthy cells that support the tumour's growth are beginning to look like an important target for cancer therapies in themselves.

It might not always be necessary to grow 3D tumours to get useful results. With the help of new techniques for growing cancer cells, for instance, a team at Massachusetts General Hospital recently tested dozens of drugs on 27 cell lines derived from people with drug-resistant lung tumours. They think the results are promising enough to try to develop the cell-line approach further.

However, the 3D approach is likely to deliver more useful insights. Cancer cells seem to grow better this way, and sometimes even show different responses to the same drugs. For instance, when Loizidou's group tested how colorectal cancer cells responded to a drug called cetuximab, which targets a protein on their cell surface, they found that the cells grown in 3D produced far more of this protein than standard cell lines, and yet despite this they were less responsive to the drug.

One way or another, then, it seems clear that we will be cloning the cancers of many more people in the future. Whether it is worthwhile for individuals to pay to have this done yet, though, is unclear.

Crawford, for instance, has not yet benefited directly. A series of post-surgical complications have made her too unwell to face further drug treatments at least for now, although on the bright side, there is currently no sign of her tumour returning. Nevertheless, for her the knowledge that the mouse avatars revealed several promising drug combinations is a source of great comfort and hope. "If I get struck again, there's at least a drug, or a couple of drugs that are likely to be effective," she says. "It means that I've got a fighting chance."

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