The breast cancer 'avatar' mice that could help personalise treatment

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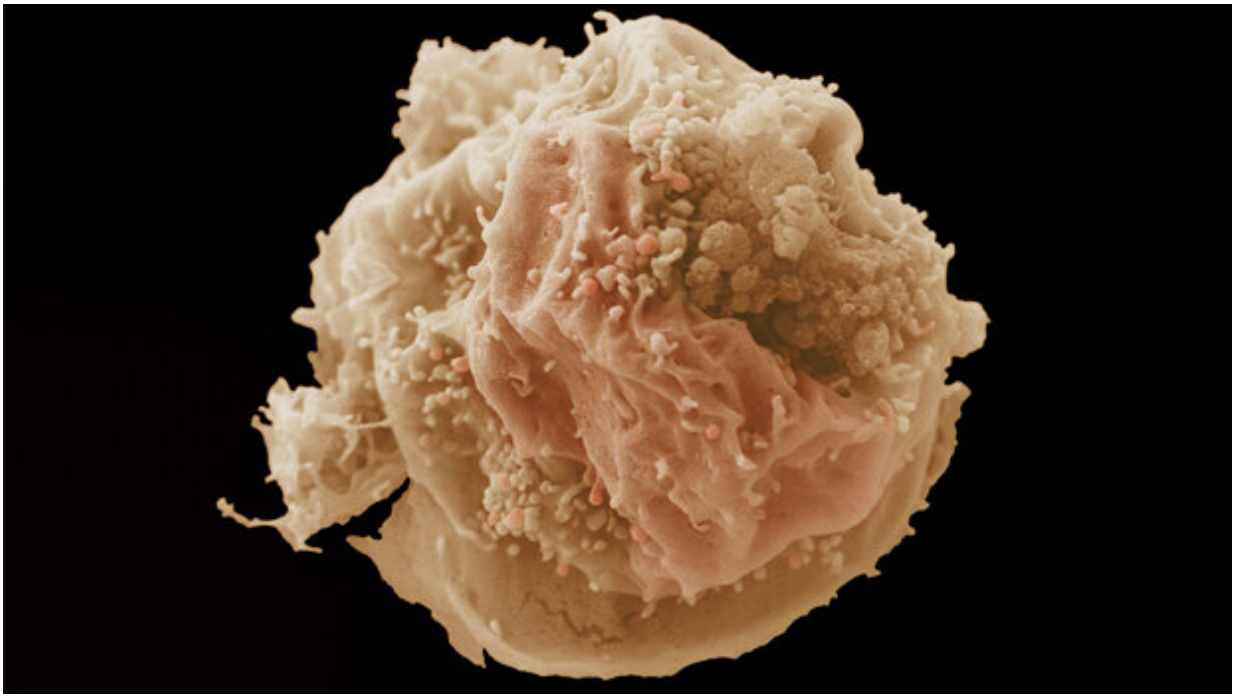

A breast cancer cell. Credit: LRI EM unit.

All cancers are different. Lung cancer is very different from breast cancer, and one person's breast cancer may be very different from another's.

This means treatment for one group of patients won't necessarily work for another. And without more accurate ways to tell who should get

which treatment in certain cases, there's the potential for unnecessary anxiety and wasted time and money.

Our breast cancer researchers in Cambridge are working to stop that.

Quick and personal decisions

Dr. Jean Abraham co-leads the Personalised Breast Cancer Programme (PBCP), a collaboration between Cancer Research UK and Addenbrooke's Charitable Trust. It has analyzed the genes of 600 breast cancer patients to see if they could do this quickly enough to use the information to guide treatment decisions.

These patients are also involved in clinical trials aiming to understand why some respond to treatment while others don't, by examining the genetic details of their individual cancers.

"The real drive is to identify those who would benefit from treatment and spare treatment from those who don't need it," says Abraham, who believes the program is already making a difference.

"It's led to changes in treatment decisions which in turn has prevented severe toxicities in some patients as they've managed to avoid drugs which they may have had problems handling. It has also led to the screening of patients' families due to previously unknown inherited cancer risk," she says.

For most patients, the results confirmed that they were receiving the best treatment available. But a small number (15 in 100) were found to be better suited to a different drug, and over half (more than 60 in 100) were found to be potentially eligible for a clinical trial should their cancer come back in the future.

"The beauty of the sequencing project is that we are getting the data faster and can react," Abraham says.

Over the next five years, the team aim to recruit 1650 more patients across the UK.

The Cancer Research UK Cambridge Institute, just a stone's throw away from Addenbrooke's Hospital, is also developing "Integrated Cancer Medicine", an approach combining genetic studies, imaging, animal and clinical data to better predict how patients' cancers might respond to treatment. The PBCP provides part of the genomic data required to develop this approach, but it's also being used by other researchers.

The 'avatar' mice that could personalise breast cancer care

Dr. Alejandra Bruna, from the Cancer Research UK Cambridge Institute, transplants tumor samples taken directly from a patient during surgery into mice, aiming to recreate the complexity of the patient's cancer in these so-called 'avatars'.

"One of the main drawbacks in cancer research has been the lack of laboratory tools that represent the true complex nature of tumors in patients," she says. "This has impacted our understanding of cancer biology and drug development, and our findings in the lab aren't always reproduced in the clinic."

These avatars are an attempt to develop more representative techniques.

Bruna's own inspiration came from realizing that every patient is different, and conversations she had with her father while he was being treated for cancer.

"I asked myself if there would ever be a way to test lots of different therapies in one given tumor, which would help us treat patients more efficiently and with less toxicity," she says.

So far, she's grown tumors from more than 100 breast cancer patients in mice, showing that they're very similar to the patient's original tumor.

"We have shown that when you put a tumor in the avatar mouse that the tumor retains all the molecular features that that tumor has in the human."

They've then gone a step further. "We've tested how that specific tumor responds to hundreds of different therapies," she says. And this is the power of the technique—patients can only be treated in one way at a time, but different treatments can be tested in multiple mice.

"We have that same tumor in many different realities," says Bruna.

Paradoxically, another motivation for Bruna is reducing the number of animals used in research. Developing more accurate techniques means fewer mice will be used in the future.

She hopes that the information from these studies could help guide clinical decision making for patients in the future. Currently they're testing whether drug responses and the tumor's behavior are the same in the patient as their very own avatars. The next goal would be to run a clinical trial to test whether avatars could be used to predict which future therapies would work best in patients whose disease has returned.

This would help doctors and patients make a more informed choice, as right now there's not a huge amount of evidence for what treatment to use when cancer comes back.

The research continues

But these techniques are expensive and need lots of infrastructure and expertise. And not all tumors transplanted into mice will grow.

One downside is that these mice lack an immune system, which has a big impact on how cancers progress and respond to treatment.

There's a lot more to do, such as setting up a clinical trial to see if using the information on avatars will benefit patients. They also need to refine which patients these avatars could help most, possibly focusing on a subset of patients with fewer treatment options.

Bruna and Abraham are hopeful this will move quickly, largely because patients have been so generous in supporting the work.

"Time and time again I'm struck by how willingly, at a very vulnerable moment in their lives, shortly after being diagnosed, patients will commit to help with multiple research projects largely to help those who come after them," Abraham says.

"This study and its legacy is really down to them."

More information: Alejandra Bruna et al. A Biobank of Breast Cancer Explants with Preserved Intra-tumor Heterogeneity to Screen Anticancer Compounds, *Cell* (2016). DOI: 10.1016/j.cell.2016.08.041

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