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New cancer models could help scientists to devise better treatments.

BIOMEDICAL SCIENCE

US cancer institute overhauls cell lines

Veteran cells to be replaced by human tumours grown in mice.

BY HEIDI LEDFORD

After more than 25 years of heavy use by researchers around the world, the US National Cancer Institute (NCI) has decided to stop screening most drugs using the NCI-60, its panel of 60 human cancer cell lines grown in culture. In late spring of this year, the institute will launch a rejuvenated repository of cancer models that are derived from fresh patient samples and tagged with details about their clinical past.

The NCI action responds to a widespread push for cancer models with a closer link to the patients they are intended to help. On 11 February, cancer researchers gathered in New Orleans, Louisiana, for a meeting hosted by the American Association for Cancer Research that focused on the creation of new models from clinical samples.

Since 1990, industry and academia have screened more than 100,000 compounds using the NCI-60, in order to study the molecular details of cancers.

When the NCI-60 was established, researchers had a very different conception of cancer, says James Doroshow, director of the Division of Cancer Treatment and Diagnosis at the NCI in Bethesda, Maryland. "Thirty years ago, the idea was that if you found a drug that worked on six breast cancer cell lines, then you could use it to treat breast cancer," he says. "Well, it doesn't work that way."

Since then, breast cancer has been broken down into subcategories that are based on genetic mutations — and each category may respond differently to treatment.

The NCI-60 cell lines have also lived for thousands of generations in culture. Over time, this has altered their genetic make-up and behaviour.

The NCI will continue to supply the NCI-60 lines to researchers, but will eventually refocus its drug screening on newer models. It is developing hundreds of 'patient-derived xenografts' (PDXs) by implanting small chunks of human tumours in mice — an environment that better mimics the human body. The tumours can then be harvested and reimplanted in other mice, allowing researchers to study a given tumour in multiple animals. The NCI will distribute cells from those PDXs, plus data on each tumour's genome sequence and gene-expression patterns, and the donor's treatment history.

The institute will also make cell lines from the samples for use in more-detailed biochemical studies and in drug screening. And it is developing cell cultures and xenografts from tumour cells that are circulating in the blood to model tumours that are difficult for surgeons to biopsy. Doroshow estimates that his team will have 75 models ready for public distribution when the repository opens; the group aims to produce 1,000 in the first phase.

The NCI effort reflects a wider trend. Sixteen European institutions have formed EurOPDX, a consortium that boasts 1,500 PDXs. The Jackson Laboratory, a non-profit company in Bar Harbor, Maine, has 450 PDXs, and another 100 in development. Many more reside in pharmaceutical companies: last year, the Swiss pharma giant Novartis published a drug screen using 1,000 PDXs (H. Gao *et al. Nature Med.* **21,** 1318–1325; 2015).

PDXs have also garnered attention as models to guide treatment of individual patients: mice bearing PDXs could serve as 'avatars' to allow physicians to screen for the most-effective treatment regimen. But the process of generating a PDX is often too slow to benefit the donor, says Edison Liu, chief executive of the Jackson Laboratory. Instead, Liu sees Novartis's approach — studying large collections of PDXs to help future patients — as more promising.

Such models can capture the genetic complexity of human cancers better than old cell cultures or genetically engineered mice, but PDXs also have shortcomings. Most are generated in mice that lack normal immune responses, to prevent rejection of the human cells. Efforts are under way to engineer mice with aspects of the human immune system, but no mouse fully captures the complexity of the system.

Despite the limitations, some researchers have translated PDX results into clinical gains. Livio Trusolino, a cancer researcher at the University of Turin in Italy, and his colleagues mined their collection of 600 colorectal cancer PDXs. They found that PDXs from some drug-resistant tumours responded better to a combination of treatments normally used against breast cancer — a result that was then borne out in a small clinical trial, Trusolino announced at the meeting in New Orleans.

"For the first time in my life, my results have been translated into a benefit for patients," Trusolino says. "It is very rewarding." ■

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