⮕ **CANCER**

Xenograft encyclopaedia identifies drug combination opportunities

Preclinical cancer drug development would benefit greatly from models and experimental approaches that accurately predict clinical responses. To this end, Gao and colleagues have generated 1,075 patient-derived tumour xenograft models (PDXs) and found that these could be a more accurate measure of the response of a population of patients than traditional preclinical tools.

Cells from patients with primary tumours in different organs were collected and propagated by serial xenograft

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transplantation in mice to generate the Novartis Institutes for BioMedical Research PDX encyclopedia (NIBR PDXE). Relative to cell lines in the Cancer Cell Line Encyclopedia, the xenograft lines in the NIBR PDXE had a lower mutation rate; the NIBR PDXE mutation rate was similar to the mutation rate in patient tumours.

These xenograft-carrying mice were then treated with one compound each using a 1x1x1 experimental design (one animal per model per treatment). A total of 38 approved or experimental therapeutic agents were tried in PDXs, either as single agents or in combinations. Many features of cell culture models and tumours in patients were also found in the PDXs; for example, the response rate of PDXs with BRAF V600 mutations to the RAF inhibitor encorafenib was similar to those observed in cell lines and in clinical trials, and known mechanisms of resistance, including *BRAF* amplification or mutations of the genes encoding MEK1 or MEK2, were observed in the PDXs in response to encorafenib treatment. Furthermore, in the PDX models, adding a small-molecule MEK inhibitor increased the response rate, in line with the results of a Phase I/II trial of this combination.
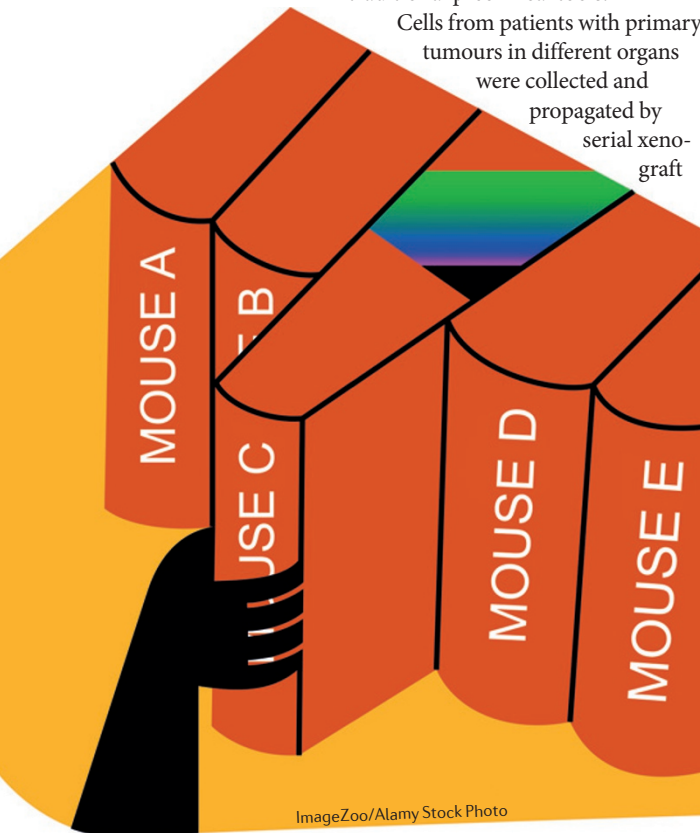
The authors investigated whether PDXs could also identify potentially useful drug combinations. Inhibitors of cyclin dependent kinase 4 (CDK4) in combination with either encorafenib or agents targeting phosphoinositide 3-kinase (PI3K) were found to increase progression-free survival more than these single agents did if used separately. Interestingly, a cooperative effect between CDK4 inhibitors and PI3K inhibitors has not been observed in previous experiments in cell culture models. Similarly, previous cell culture experiments had indicated that inhibitors of insulin-like growth factor 1 receptor (IGF1R) or mammalian target of rapamycin (mTOR) potentiated the activity of multiple targeted therapies, but this effect was not observed in the PDXs in this study. Of note, combining IGF1R inhibitors or mTOR inhibitors with other targeted agents has had disappointing results in the clinic, in line with the results in the PDXs.

The NIBR PDXE could be a useful tool in preclinical drug development and to optimize the use of existing drugs, particularly if further studies validate or refine the increased accuracy of these models in predicting patient responses to drug combinations.

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ORIGINAL RESEARCH PAPER Gao, H. *et al.* High-throughput screening using patient-derived tumor xenografts to predict clinical trial drug response. *Nat. Med.* **21**, 1318–1325 (2015)