A precision approach to tumour treatment

Progress is being made in the use of personalized approaches to create both in vitro and in vivo tumour models that could be used to aid cancer drug–treatment decisions and increase our understanding of how tumours respond to therapy.

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Precision cancer therapy pairs the latest insights into tumour biology with cutting-edge technologies to identify gene alterations that can be directly matched to anti-cancer agents. Writing in *Cancer Discovery*, Pauli et al.1 outline how they have opened another chapter of this work by using DNA sequencing of tumour samples along with testing of patient-derived cellular models. This enables the use of high-throughput drug screening to assess treatment-response patterns and thereby expand the options for tailoring cancer therapy to the individual.

Pauli and colleagues initiated a clinical-research programme that sequenced the DNA of protein-coding regions of the genome in samples of individual patient’s tumours, as well as their healthy tissue for comparison, to identify tumour-specific alterations that might be drug targets. However, the authors soon realized that DNA-sequence information alone was insufficient to guide therapeutic decision-making in most cases. Of the 501 people with cancer who were tested, the majority of whom had advanced-stage disease, only around 10% had gene alterations that could be directly matched to targeted agents approved by the US Food and Drug Administration (FDA). This percentage included those whose tumours might be targeted through ‘off-label’ drug use, in which a treatment approved to target cancer-associated mutations that can be directly matched to targeted agents approved by the US Food and Drug Administration (FDA).

This prompted Pauli et al. to try another way of identifying potentially effective matches between tumours and drugs. They used organoids — cellular structures grown in *in vitro* 3D cell-culture systems that retain interactions both between cells and between cells and the extracellular matrix that surrounds them. These cultures, derived from the patients’ tumour cells, offer better preservation of the biological characteristics of tissues than do the more commonly used monolayer cell cultures. Organoids provide a large-scale platform for drug-sensitivity screening that offers an acceptably fast turnaround time, which could enable clinical application on the basis of results obtained.

Using organoids, Pauli et al. tested a comprehensive library of nearly 160 compounds, enabling them to identify effective and drug combinations that limited cancer-cell growth. Their findings were validated *in vivo* by transplanting organoid cells into immunodeficient mice to generate personalized models known as patient-derived xenografts (PDXs), a gold standard for the preclinical evaluation of cancer therapeutics (Fig. 1). Pauli and colleagues’ study offers one of the first examples of an organoid-based approach that uses high-throughput drug screening along with validation of the drugs in PDXs derived from the same organoids.

From 145 specimens comprising 18 different tumour types, the authors generated 56 organoid cell cultures and 19 PDX models from biopsies of either primary tumours or tissue samples of cancer cells that have migrated to other locations, known as metastases. The results of tumour DNA sequencing, high-throughput drug dose-response testing in organoids and PDX validation of the results are described in detail for four patients. Effective targeted drugs were identified *in vitro* and, on the basis of results of secondary drug screens, optimal combination regimens were selected for validation *in vivo*. However, it is important to note that the individual proposed regimens were not tested in patients, and so the investigators could not show that their selected drug hits are active clinically. The authors also recognize that the difficulties with off-label access

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**Figure 1 | Personalized tumour treatment.** Pauli et al.1 investigated a way of selecting personalized drug treatments for people who have cancer. When tumour DNA from patients was sequenced to identify tumour-specific alterations, only around 10% of the tumours in their study had an alteration associated with a drug treatment available for standard use in the clinic. To identify drug-treatment options for the tumours not associated with known drug targets, the authors established *in vitro* 3D cellular cultures of tumour cells known as organoids. These cells were used for high-throughput drug screening to identify molecules that limited cancer-cell growth. Identified drug hits were validated using mouse models that contain transplanted organoid cells known as a patient-derived xenograft (PDX). This approach generates possible treatment options to target an individual’s tumour. The proposed treatments were not tested in patients in this study.
to approved or experimental agents remains a substantial challenge that limits clinical testing based on the data obtained from this type of precision-medicine platform.

The feasibility of using patient-derived tumour samples for high-throughput drug sensitivity assays, and their integration with genomic profiling for drug repurposing, has been demonstrated previously, in a study that focused on leukaemias that were unresponsive to chemotherapy. In an off-label compassionate-use setting (in which individuals who have life-threatening conditions are given access to unlicensed drugs outside a clinical trial), the individuals with leukaemia received combinations of targeted agents predicted to be effective from drug-sensitivity screenings, and there were promising reports of short-term responses. However, the authors of that paper also found evidence that as leukaemia progressed in patients, tumours became resistant to those agents tested in vitro and potentially vulnerable to others, and DNA sequencing revealed a diverse set of gene alterations associated with disease progression.

The ability to use tumour-based drug-screening platforms to accurately predict clinical responses relies on the cultured cells retaining the complex molecular and biological characteristics of the tumours from which they are derived. Although cancer DNA and transcriptional profiles are reasonably well conserved in preclinical cellular models when compared with the patients’ original tumours, there are differences in immune and vascular microenvironments. Drugs that inhibit immune-system checkpoints and interactions between tumour cells and their surrounding cells, known as stromal cells, would not be identified using organoids derived only from cancer cells.

Furthermore, organoids usually have high expression of genes involved in responses to contact with foreign substances, and of genes involved in metabolic processes that might possibly affect cancer-cell growth and survival. Moreover, a drug response observed in an organoid might not guarantee a response in patients, given the differences in the processes that activate drug molecules in preclinical models and in humans. In addition, the half-life of compounds and their peak concentration at a tumour site can vary greatly when comparing in vitro and in vivo experiments.

Yet despite these variations, which can be crucial when selecting the optimal model system for drug screening, the drug-response patterns observed were fairly consistent between organoids and PDX systems in the studies by Pauli et al. and others. Future technological advances might improve our ability to predict clinical outcomes. Such advances might include organoid experiments that incorporate a variety of different cell types, such as stromal cells, to mimic an in vivo microenvironment, as well as more ‘humanized’ PDX models of immunodeficient mice that contain human immune cells, which could facilitate research aimed at advancing immune-based therapies.

We believe that the real potential of patient-derived organoid libraries will be revealed when investigators generate large shared databases that allow the study of complex correlations between tumour genomics and drug sensitivities, and the identification of combinations of targeted agents that might perform better than the most commonly used standard chemotherapies for certain tumours. Clinical responses to single-agent targeted therapies that have been selected because of specific gene alterations are usually short-lived, and in most cases the most effective drug combination cannot be chosen on the basis of DNA-sequencing results and published cancer research.

Two types of correlative analyses could prove particularly insightful once many cases have been profiled and this combined ‘big data’ becomes available for modelling. The first would be a cross-comparison of drug-response metrics for agents with different mechanisms of action. Clusters of drugs that have highly correlated patterns of sensitivity across samples could anchor combination therapies, despite the underlying genomic and transcriptional variability in any given tumour. The second would be to correlate drug sensitivities with tumour genomics. Drug combinations with a synergistic effect might then be selected even when only genomic data are available.

The precision-medicine approach described by Pauli et al. might help to bridge the existing gap between an understanding of cancer genomics and the development of personalized therapy design. Although this type of approach has only been tried in a few research institutions, use of an organoid high-throughput screening platform has enabled the discovery of unexpected drug targeting of certain tumour-associated alterations. This approach has allowed the identification of tumour drug-sensitivity matches that are being assessed in clinical trials.

To facilitate broader clinical implementation of this approach, the success rate for establishing organoids from tumour samples needs to be improved, and alternative sources of tumour cells (such as from blood samples) must be investigated to avoid relying on repeated biopsies of metastases in individuals who have solid tumours. When paired with genomic analyses conducted over time to understand the evolution of drug-sensitive and drug-resistant clones, organoid drug-screening technology might pave the way for optimal truly personalized, adaptive and dynamic treatments for advanced-stage cancers.

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