ANTICANCER DRUGS

# Finding the perfect combination

Molecularly targeted drugs have had a substantial impact on cancer treatment, but patients eventually develop resistance to these agents. Now, reporting in *Science*, Benes, Engelman and colleagues present the development of a pharmacogenomic platform for the identification of drugs that resensitize resistant tumours, thereby shedding light on resistance mechanisms and informing personalized combination therapies.

The study focused on non-small-cell lung cancers (NSCLCs) that harbour activating mutations in *EGFR* or *ALK*, which are routinely treated with specific tyrosine kinase inhibitors (TKIs). Resistance usually develops within 1–2 years, through a variety of mechanisms — for example, mutations can prevent target inhibition by the TKI ('gatekeeper' mutations) or activate compensatory signalling pathways ('bypass track' mutations). Cells that have developed bypass track resistance are insensitive to drugs targeted at either the driver oncogene or the components of the compensatory signalling pathway; however, they are sensitive to a combination of these drugs.

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To examine mechanisms of resistance and identify effective drugs, the authors generated cell lines directly from tumour biopsies — a process facilitated by recent advances in cell culture methods. The cells were then subjected to a screen that combined the original TKI (against which cells had become resistant) with a panel of 76 drugs targeted at key regulators of cell proliferation and survival. Proof-of-principle was generated using five cell lines for which the mechanisms of resistance were known; the screen successfully identified the inhibitors of the known compensatory signalling pathways. The system was then tested in 55 NSCLC cell lines that had acquired resistance of unknown mechanism. 20 of these cell lines were directly derived from patients who had progressed on ALK or EGFR inhibitors, and the remaining cell lines were generated *in vitro*.

The screen identified a number of previously undescribed mechanisms of resistance — for example, a cell line derived from an *ALK*-mutated cancer was resensitized to ALK inhibitors when these were combined with a MET inhibitor. This had not been previously described, and was not found for any of the other *ALK*-mutated cancer cell lines, illustrating the power of this approach for developing personalized therapies. Moreover, the pharmacological screen identified resistance mechanisms that would have been difficult to decipher by genetic analysis alone — for example, it was found that *ALK*-mutated NSCLCs often exhibit upregulated SRC signalling, without any evidence of mutations in *SRC*. Several combination therapies identified for specific cell lines were subsequently tested in xenograft models using the same cells and shown to be effective, indicating that the test may indeed be predictive for *in vivo* activity.

The authors caution that both the success rate of cell-line generation from biopsy specimens (50% in this study) and the time scale for establishing cell lines (2–6 months) will need to be improved for this approach to become clinically useful. However, once optimized, it may be used not only for NSCLC but also for other types of cancer, allowing truly personalized cancer therapy.

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