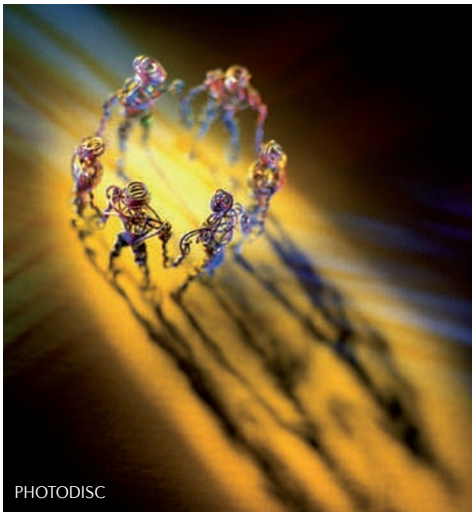
DRUG SCREENING

Shedding light on tumour–stroma interactions


PHOTODISC

The effects of a tumour's microenvironment can adversely affect the activity of chemotherapeutic agents and lead to what is referred to as stroma-induced chemoresistance. In *Nature Medicine*, Mitsiades and colleagues describe a new drug-screening platform that quantitatively measures the effects of stromal cells on anticancer drug activity. Its scalability for high-throughput screening could detect stromal-cell-mediated drug resistance at early stages of anticancer drug development.

The tumour-cell-specific *in vitro* bioluminescence imaging (CS-BLI) assay involves co-culturing tumour cells that stably express luciferase with non-malignant stromal cells. The bioluminescent signal that is recorded is proportional to tumour cell viability, so the effects of anticancer drug treatments in the presence or absence of stromal cells can be assessed.

The authors validated the screening method with agents known to be affected by interactions with the tumour microenvironment, such as doxorubicin and imatinib (Gleevec/Glivec; Novartis). For both drugs, activity was lower when multiple myeloma or certain leukaemia cell lines were cultured in the presence of stromal cells. Interestingly, the activity of the recently US FDA-approved agent bortezomib (Velcade; Millennium Pharmaceuticals) was not affected, which is consistent with its reported capacity to overcome stromal-cell-mediated drug resistance in preclinical studies.

To gain insight into the mechanism through which stromal cells can cause drug resistance, the authors used antibodies to neutralize interleukin-6, one of the main cytokines secreted by stromal cells, which promotes tumour cell growth and survival. Although the antibodies suppressed the stromal-cell-induced resistance of multiple myeloma cells to doxorubicin, they did not completely restore the drug's activity, suggesting that other mechanisms contribute to stromal-cell-mediated drug resistance.

Examination of the molecular profile of multiple myeloma cell lines interacting *in vitro* with stromal cells revealed an upregulation of genes involved in cell proliferation, survival and drug resistance. This stromal-cell-responsive gene signature correlated with the clinical outcome of patients with multiple myeloma treated with dexamethasone (another drug that is susceptible to stromal cell drug resistance), highlighting the need for agents that are able to prevent the effects of stromal cells on tumour cells.

When the authors carried out a screen of more than 3,000 compounds for anticancer activity, they found that a large proportion of them were less active in the presence of stromal cells than in their absence. However, a small fraction of the compounds tested, including the aminopurine reversine, were actually more active in the presence of stromal cells. The effect of reversine was confirmed in mice, as the compound was able to decrease the tumour burden in a diffuse tumour lesion model (in which tumour cells interact with stromal cells) more effectively than in a subcutaneous tumour model (in which these interactions do not take place).

By using specific combinations of tumour and accessory cells, the CS-BLI assay will allow researchers to assess the effects of particular tumour microenvironments on anticancer drug activity at preclinical stages and therefore potentially reduce the rate of attrition of compounds in clinical trials.

Monica Hoyos Flight

ORIGINAL RESEARCH PAPER McMillin, D. W. *et al.* Tumor cell-specific bioluminescence platform to identify stroma-induced changes to anticancer drug activity. *Nature Med.* **16**, 483–489 (2010)