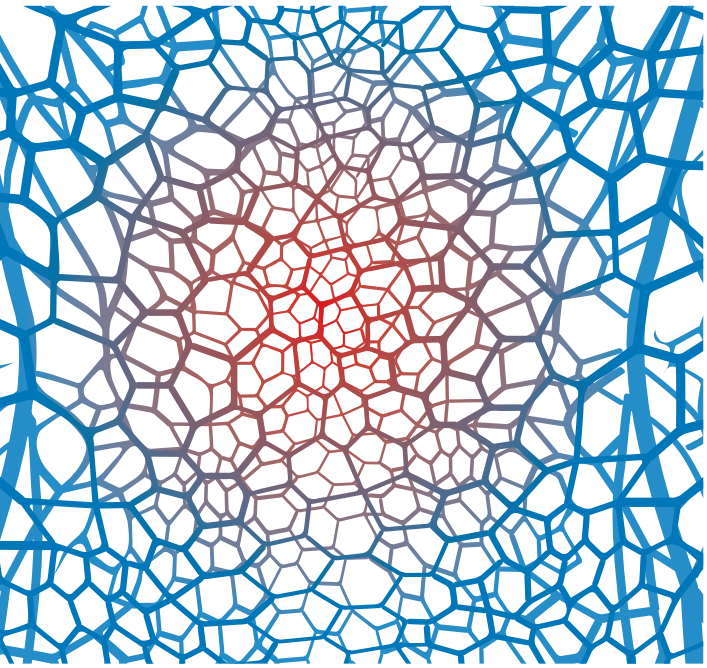
ANTICANCER DRUGS

Using CTCs to test drug sensitivity

> patient-derived CTCs could be used to test potential therapeutic regimens

Circulating tumour cells (CTCs) have alterations that are reminiscent of the solid tumour from which they are shed, indicating that they could be used diagnostically and to monitor disease progression. Now, a team led by Shyamala Maheswaran and Daniel Haber has shown that some CTCs can be cultured *in vitro* and used to track the evolution of the primary tumour and to screen drugs to identify the most effective therapy.

Yu *et al.* used a microfluidic device called CTC-iChip, which removes blood cells from patient blood samples and leaves behind intact CTCs that have not been selected according to cell surface marker. Using blood samples from patients with metastatic oestrogen receptor (ER)-positive breast cancer, they isolated CTCs and found that some grew out in culture, the optimal conditions being non-adherent conditions in serum-free media supplemented with epidermal growth factor (EGF) and fibroblast growth factor 2 (FGF2), in 4% O_2 (hypoxia). They were able to generate oligoclonal CTC cultures for >6 months from 6 of 36 patients and the CTC lines shared features with matched primary CTCs, although one line lost ER expression and all CTC lines were more proliferative than primary CTCs.



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Next, the authors assessed whether the CTC lines could form tumours in immunodeficient NSG mice. Three of the five CTC lines that were tested formed tumours, which shared features with matched patient tumours. Mutation analysis of primary tumours and CTC lines revealed that they share some genetic alterations, whereas the CTC lines had additional mutations that the metastatic tumour deposits had acquired during disease progression. One-half of the CTC lines had activating mutations in *ESR1* (which encodes ERα), which have been reported to occur in patients treated with aromatase inhibitors for long periods of time, consistent with patient history. The authors also detected many other mutations that they were able to confirm from sequencing of CTC lines established from CTCs isolated from serial blood samples from patients during disease progression.

The authors then turned their attention to the possibility of using the CTC lines to test therapy with standard drug regimens and drugs under development. Reassuringly, they found that some of the CTC sensitivities to drugs correlated with patient history. They also found that STA9090, a heat shock protein 90 (HSP90) inhibitor, was toxic to *ESR1*-mutant CTCs as monotherapy or in combination with the ER modulators raloxifene or fulvestrant. Low-dose STA9090 suppressed ER levels in primary tumour cells with mutant *ESR1* but had no effect on cells with either wild-type *ESR1* or low-frequency *ESR1* mutations. The reason for this was proposed to be that mutant ERα is more dependent on HSP90 for stability than wild-type ERα. Their drug screen also revealed that a combination of STA9090 and the PI3K inhibitor BYL719 had cooperative effects in *PIK3CA*-mutant CTCs. BYL719 that was combined with the FGF receptor 2 (FGFR2) inhibitor AZD4547 in a CTC line that was found to have activating mutations in *PIK3CA* and *FGFR2* also had cooperative effects *in vitro* and abrogated the growth of established xenografts from this CTC line.

Thus, patient-derived CTCs could be used to test potential therapeutic regimens to more efficiently 'personalize' patient treatment.

Gemma K. Alderton, Senior Editor
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