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► **COVER:** 'Unwinding' by Lara Crow, inspired by the Review on p644.



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Therapeutic resistance is emerging as an important concern in the care of patients with cancer, and it is hoped that understanding the factors that lead to both intrinsic and acquired resistance will help researchers to develop more effective cancer therapies. In July, we launched a series of specially commissioned articles on therapeutic resistance, and in this issue we bring you two more articles in this series.

On page 631, Elizabeth Musgrove and Robert Sutherland review the biological determinants of resistance to endocrine therapies in breast cancer, focusing specifically on tamoxifen, the endocrine therapy for which clinical data are most extensive. As many as one-quarter of breast cancers may be resistant to endocrine therapies, so there is an urgent need to develop biomarkers that can predict whether a patient will respond to endocrine therapy and to identify new therapeutic targets for endocrine-resistant breast cancer. As the authors discuss, genomic, proteomic and functional screening tools provide us with important new insights into endocrine resistance.

In addition to changes within a tumour cell, the tumour microenvironment can influence resistance to therapy; this is termed environment-mediated drug resistance. In this process, stromal cell-derived signalling and adhesion to the extracellular matrix provide tumour cells with protection from therapy-induced apoptosis. Surviving tumour cells in this microenvironment can then develop acquired resistance, leading to disease relapse. On page 665, Mark Meads, Robert Gatenby and William Dalton present their perspective on this important aspect of therapeutic resistance and propose that this interaction between the tumour cells and their microenvironment should be targeted as an adjuvant to chemotherapy regimens to prevent the emergence of cells with acquired resistance and relapse.

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