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► **COVER:** 'Targeting apoptosis' by Susanne Harris, inspired by the Apoptosis Focus articles.



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**U**nderstanding of the molecular mechanisms of apoptosis and the role of its dysregulation in numerous diseases has advanced significantly in the past decade. This month, with the aim of highlighting the potential of harnessing such advances for therapeutic purposes, we present a special focus on apoptosis. In our first Review, Colman and colleagues discuss the BCL-2 family of proteins, focusing on their validation as cancer targets and recent progress in the development of antagonists of pro-survival proteins in this family. Another protein with anti-apoptotic activity, which is frequently found to be overactive in cancer, is NF- $\kappa$ B. Conversely, the tumour suppressor p53, which activates a key apoptotic signalling pathway, is often mutated and inactivated in cancer. Lane and colleagues discuss crosstalk between these two pathways, reviewing candidate small molecules capable of simultaneously activating p53 and inhibiting NF- $\kappa$ B, thereby promoting cancer cell apoptosis. In their Perspective, Bond and colleagues consider therapies being developed to target p53, and discuss how knowledge of genetic variations of p53 pathway components — in particular p53 itself and its negative regulator MDM2 — may be used to tailor the use of such agents. Another promising therapeutic approach to target cancer cells that have avoided apoptosis is through activation of so-called death receptors, as this might circumvent some of the most common anti-apoptotic mutations in such cells, and the development and potential of pro-apoptotic receptor agonists are reviewed by Ashkenazi. Finally, Reed and colleagues discuss the roles of endoplasmic reticulum stress-initiated cell death pathways in diseases including cancer, neurodegeneration, heart disease and diabetes, highlighting novel therapeutic strategies. All of the articles in the focus will be freely available online at [www.nature.com/nrd/focus/apoptosis](http://www.nature.com/nrd/focus/apoptosis) for 6 months thanks to the support of Genentech, Inc.

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