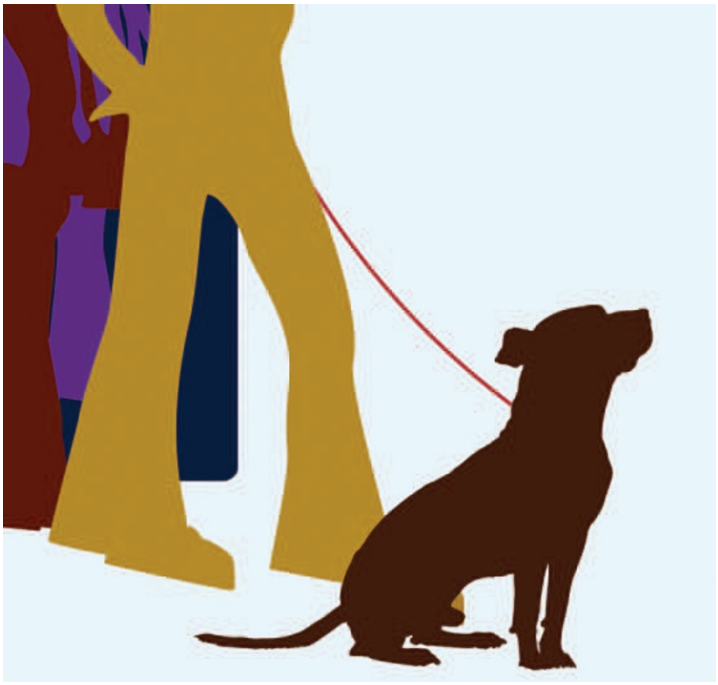
ANTICANCER DRUGS

Unleashing p53



The transcription factor p53 controls a key pathway protecting cells from malignant transformation. In many cancers, however, this protective activity is switched off, commonly as a result of overexpression of the protein MDM2, which binds to the transactivation domain of p53 and blocks its ability to activate transcription. So, inhibiting the binding of MDM2 to p53 has been suggested as an anticancer strategy, a proposal that is given support by a recent paper in *Science* describing small-molecule antagonists of the MDM2–p53 interaction that activate the p53 pathway in cancer cells and inhibit tumour growth in mice.

Protein–protein interactions have traditionally been viewed as highly challenging targets for small-molecule drug discovery, owing to issues such as the lack of well-defined binding pockets at the interface. However, the crystal structure of MDM2 bound to a peptide from the transactivation domain of p53 revealed that MDM2 possesses a relatively deep pocket that is filled by a helical region of the p53 peptide, raising the hope of identifying small molecules capable of binding in the pocket instead of p53. Vassilev and colleagues therefore screened a diverse library of compounds for their ability to inhibit the binding of MDM2 to p53, and discovered a series of *cis*-imidazoline analogues that displace p53 from its complex with MDM2 with IC_{50}s in the nanomolar range. A crystal structure of one of the compounds in complex with MDM2 confirmed that it bound in the p53-binding site.

Testing the imidazoline analogues in a range of cancer-cell-based assays provided strong evidence that they activated the p53 pathway, leading to cell-cycle arrest and apoptosis. Encouraged by this, the authors assessed whether one of the analogues could suppress the growth of established tumour xenografts in mice. Oral administration of the compound, which was well-tolerated, resulted in 90% inhibition of tumour growth relative to vehicle controls, compared with 81% inhibition using intravenous administration of the maximal tolerated dose of the traditional cytotoxic drug doxorubicin.

Although ~50% of human tumours have lost wild-type p53 and so would not be expected to be affected by inhibitors of the p53–MDM2 interaction, the authors' experiments indicate that activating the tumour suppressor capability of p53 with such compounds might be beneficial in the other ~50% of cancers in which the wild-type form of p53 is retained. More generally, their demonstration that a protein–protein interaction can be successfully targeted by small-molecule inhibitors provides encouragement for the growing number of research programs pursuing this challenging goal.

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References and links

ORIGINAL RESEARCH PAPER Vassilev, L. T. *et al. In vivo* activation of the p53 pathway by small-molecule antagonists of MDM2. *Science* 2 Jan 2004 (doi: 10.1126/science.1092472)
FURTHER READING Chène, P. Inhibiting the p53–MDM2 interaction: an important target for cancer therapy. *Nature Rev. Cancer* **3**, 102–109 (2003)