Controlling p53

DAVID LANE, Dundee University of Dundee, Scotland and Cyclacel Ltd.

25 years after its first description the p53 protein has been shown to play a key role in both cancer and aging. The p53 protein is activated by many different stress pathways, including oncogene action and DNA damage. The elucidation of the p53 response, which is aberrant in most cancers, (including breast, lung, stomach and colorectal cancer) has provided many new targets for drug development and p53 gene therapy is now approved in China. In tumours where p53 is mutant small molecules may be able to restore its function. In many tumours the wild type p53 gene remains intact but its function is compromised by loss of upstream signalling pathways or downstream effectors. A key regulator is Mdm2, an E3 ubiquitin ligase, that binds and ubiquitinates p53 and directs its degradation via the proteosome. Small potent peptides that can block the p53 Mdm2 interaction and activate the p53 response have been described. Growing selections of lead small molecules that mimic the action of these peptides have also been recently discovered. Cell based screens have revealed that inhibitors of nuclear export and inhibitors of transcription (one of which is in clinical trial) can also activate the p53 response therapeutically. The pharmaceutical regulation of the p53 pathway offers great hope for improved treatment of human cancer.