

## THE P53 PATHWAY

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### Abstract

Somatic mutations in the p53 gene occur in half of all human cancers and germ line mutations in p53 are responsible for the family cancer predisposition known as Li-Fraumeni Syndrome. In those cancers that retain the normal p53 gene other components of the p53 pathway are often damaged. Recently two mouse models have suggested that p53 activity may also affect aging. The p53 response is induced by a wide variety of different stress signals and when activated can induce cell cycle arrest, cell senescence or cell death. Many currently used cancer treatments activate the p53 response through a DNA damage dependant pathway, and p53 gene therapy has recently gained clinical approval in China . In mice and men the threshold of the response is very finely balanced and controlled by a number of regulatory proteins. Of particular interest is the Mdm2 protein, a ubiquitin E3 ligase that binds to p53 and targets it for degradation. A recently discovered polymorphism in the Mdm2 promoter may affect the age of onset of cancer in man. Drugs that target the Mdm2 pathway can act as non-genotoxic activators of the p53 response and one of these is currently in clinical trial in Singapore.

Understanding in detail how the p53 response is regulated may allow the pharmaceutical manipulation of the pathway. We have very recently discovered that the p53 gene has a more complex structure than has been appreciated for the last twenty years and several new iso-forms of p53 have been characterized potentially yielding new sources of individual variation and new targets for therapy.