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LABORATORY–CLINIC INTERFACE

Transgenic models and cancer treatment

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Introduction

The ability to manipulate the mouse genome using transgenic technology has led to the production of many transgenic models of human cancers and other genetic diseases. These animal models provide a unique resource for investigating in an intact animal the molecular basis of tumour formation and malignant progression. They are also valuable for assessing the mechanism(s) of action of existing cancer treatments, for establishing the efficacy of new drugs, and for developing gene therapy strategies either to inhibit aberrant oncogene activity or to restore tumour suppressor function. However, construction of the transgenic animal model is only a first step in understanding the disease state and drug development, and gene therapy strategies will continue to depend upon a thorough analysis of the transgenic phenotype at both the cellular and molecular levels.

Transgenic technology

The first transgenic animal models were based on the direct microinjection of a DNA construct into the pronucleus of a fertilized egg (1–3). This approach can be used to generate gain-of-function mutants in which a gene is overexpressed from its own promoter or can be directed to give ubiquitous or tissue-specific ectopic expression using heterologous promoters. Constructs containing genes carrying an engineered mutation can also be injected, thereby determining whether or not a given gene product can exert an effect in a dominant manner. The success of this type of approach is dependent upon obtaining high levels of expression from the DNA construct and, when requiring cell or tissue-specific expression, on the availability of a suitable promoter to direct gene expression to the appropriate site.

The technology to produce loss-of-function mutations was developed and demonstrated in the targeted deletion of the *Hprt* gene using homologous

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