S6. The Cancer Genome Project

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Identification of the genes that are mutated and causally implicated in oncogenesis has been a central aim of cancer research over the last two decades. However, many more cancer genes exist and it is anticipated that the human genome sequence will facilitate identification of the remainder.

Identification of homozygous deletions has been the critical step in the discovery of most tumour suppressor genes/recessive oncogenes that have been found through analysis of somatic changes (as opposed to those which have been identified by genetic linkage analysis and positional cloning using familial cancer clusters). Thus the identification of RB1, PTEN, SMAD4, SNF5/INI1, and p16 were all contingent upon finding key homozygous deletions. We are currently investigating the presence of large homozygous deletions by PCR amplification of a series of increasingly dense Sequence Tagged Site (STS) maps in a large collection of publicly available cancer cell lines and xenografts. To date over 80 homozygous deletions have been identified. The genes in these regions are being screened for telltale small intragenic mutations that will identify new cancer genes.

The second, larger, project involves screening every gene in the genome for the presence of somatic small intragenic mutations (base substitutions and small insertions/deletions) that may result in the inactivation of tumour suppressor genes or activation of dominantly acting oncogenes. Such mutations in dominantly acting oncogenes (for example ras or beta-catenin) are essentially invisible to any other method of localisation or detection. We have developed a high throughput mutation detection system based on the analysis of heteroduplexe DNA molecules on ABI3100 capillary DNA sequencers. This platform is being used to screen every gene in the genome in a set of 96 primary tumours. It is anticipated that this will take between 3 and 5 years.

Following the identification of mutations in a putative cancer gene, the gene and mutated versions will be entered into a program of functional evaluation. The aims of these studies will be to provide biological confirmatory evidence of the role of mutated genes in cellular transformation, to give a broad indication of potential function and to provide the initial stages of validation as drug targets.