URLs

MUTAGENESIS

She hops in beauty

A new functional genomics tool finally puts mice on a par with flies, worms and plants — thanks to the work of two groups who have adapted a fish transposon to hop around in the DNA of mouse somatic cells.

The dormancy of the aptly named *Sleeping Beauty* transposon came to an end in 1997, when it was engineered to be active in higher eukaryotic cells. Two groups have now turned this still rather dozy transposon into an effective mutagen, and have used it to explore cancer-related genes and pathways. DNA transposons are ideal mutagens — they have short recognition sites and, apart from a source of transposase, they require few host factors to be able to move about. The main limitation of the existing activated *Sleeping Beauty* is its low rate of transposition, which the two new studies have turned around.

Adam Dupuy and colleagues have optimized the design of *Sleeping Beauty* by cutting down its size, improving the recognition site for the transposase and incorporating sequences — for example, splice acceptor and splice donor sites — that alter the expression of genes that the element jumps into. Furthermore, expressing the transposase at higher levels enhanced its mobilizing activity.

As hoped, crossing the enzyme and the element into the same animals induced many tumours of different types. Furthermore, the transposons seem to insert randomly

into the genome and, because they are jumping more frequently, to venture far away from their original site. The transposon that was engineered by Collier, Carlson and colleagues was specifically designed to induce activating and inactivating mutations in the genes it traps, and was also effective in generating tumours, although this study focused on solid tumours that were generated in a sensitized background.

So the system works, and the mutation profile of the tumours revealed the involvement of known mutations (such as those in *Braf* or *Notch1*) and pathways, as well as interesting new candidate genes and interactions.

The potential for using DNA transposons in mice mutagens is immense, not to mention the possibility of extending the technology to other organisms. The prospect of carrying out forward genetic screens and of using the transposons as gene-therapy vectors is attractive, but ultimately the hope is that it will be possible to restrict the expression of the transposon to certain groups of cells to reveal genes that underlie tissue-specific cancers.

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References and links

ORIGINAL RESEARCH PAPERS

Dupuy, A. J. *et al.* Mammalian mutagenesis using a highly somatic *Sleeping Beauty* transposon system. *Nature* **436**, 221–226 (2005) | Collier, L. S. & Carlson, C. M. *et al.* Cancer gene discovery in solid tumours using transposon-based somatic mutagenesis in the mouse. *Nature* **436**, 272–276 (2005)

FURTHER READING Carlson, C. M. & Largaespada, D. A. Insertional mutagenesis in

mice: new perspectives and tools. *Nature Rev. Genet.* **6**, 568–580 (2005)