In the news

FRUIT BEARS FRUIT

Research originally aimed at improving fruit harvests has provided a potential anti-angiogenic therapy.

Oded Shoseyov and colleagues at the Hebrew University of Jerusalem were using the actin-binding protein actibind from *Aspergillus niger* to inhibit pollen tube formation in peaches and nectarines. Such activity decreases the number of fruits on a plant and therefore increases the size of the remaining fruit. However, the approach was not commercially viable as manual pruning remained cheaper.

Instead, the group changed tack — "In the course of our work, we started to get deeper into the science and understand how the actibind inhibits growth" said Shoseyov (http://www.israel21c.org, 15 July 2006). "We hypothesized that since the mechanism of growth is very similar — between the pollen cell and the cancer cell — that the protein would have the same effect" (http://www.reuters.com, 2 July 2006).

In cell culture and animal models actibind therapeutically inhibited angiogenesis, and, importantly, was not toxic to normal cells. "Both *in vitro* and *in vivo*, we've shown that actibind has an anticancer effect" said Shoseyov (http://www.israel21c.org, 15 July 2006). Interestingly, a human homologue of actibind, ribonuclease T2, is found in a region of chromosome 6 that is often deleted in cancer.

Asked whether he would be returning to his agricultural roots, Shoseyov said "It's definitely going to be cancer from now on" (http://www.israel21c.org, 15 July 2006).

Patrick Goymer

DRUG RESISTANCE

A taxing problem

> a previously uncharacterized gene, *Txr1*, which encodes a nuclear protein, was upregulated fivefold in cells with resistance to paclitaxel.

Taxanes are clinically used anticancer drugs that interact with β-tubulin, so blocking cell cycling and causing apoptosis. Upregulation of the multidrug transporter P-glycoprotein and mutations that interfere with the binding of taxanes to microtubules are known causes of resistance to taxanes. Chih-Jian Lih and others in the laboratory of Stanley N. Cohen have now discovered a gene called taxol resistance gene 1 (*Txr1*), which downregulates production of the apoptosis-inducing protein thrombospondin 1 (TSP1) and causes resistance to taxanes.

The authors used a function-based screen to search for genes whose alteration yielded resistance to the taxane paclitaxel (Taxol) in a taxane-sensitive prostate cancer cell line, M2182. They found that a previously uncharacterized gene, *Txr1*, which encodes a nuclear protein, was upregulated fivefold in M2182 cells with resistance to paclitaxel. When the expression of *Txr1* was reduced using small interfering RNAs, cells showed a 75–80% decrease in survival in the presence of paclitaxel.

What is the mechanism that underlies taxane resistance by TXR1? Gene-expression profiling showed that the most upregulated transcript was *Txr1*, whereas the most downregulated transcript was *Tsp1*. To investigate the relationship between TXR1, TSP1 and taxane cytotoxicity in cancer cells, the authors analysed NCI-60 cancer cell lines for which both taxane-sensitivity data and gene-expression data were available. In 13 out of 19 cell lines tested taxane cytotoxicity showed a negative correlation with *Txr1* expression and a positive correlation with *Tsp1* expression. The use of a luciferase reporter fused to the *Tsp1* promoter confirmed that *Txr1* negatively

MELANOMA

Compare and contrast

Tumour cells are characterized by many genomic aberrations, so finding those that are instrumental to tumorigenesis is difficult. Lynda Chin and colleagues have compared the amplifications in different mouse melanoma lines to narrow down the search, and have identified *Nedd9* (neural precursor cell expressed, developmentally downregulated 9) as a metastasis gene.

The authors generated two metastatic variants from a non-metastatic mouse model of melanoma. Profiling the genomic DNA of these variants showed that they both had amplifications on chromosome 13 relative to the parental control. The shared region, which was amplified in both lines, was 850 kb and contained 8 genes.

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To identify the key gene in the amplified region, expression patterns of these 8 genes were studied in a range of metastatic melanoma and non-transformed melanocyte cultures. *Nedd9* was the only gene that was consistently upregulated in the melanomas but not in the melanocytes. This pattern was also found in human melanoma samples.

To validate *Nedd9* as a candidate metastasis gene, RNA interference was used to knock down *Nedd9* expression in the original melanoma lines. A 90% reduction in expression resulted in up to a 75% reduction in metastatic potential. Conversely, in an HRAS-overexpressing non-metastatic background, overexpression of NEDD9 led to metastasis.

So, how does NEDD9 cause this effect on metastasis? The authors