In the news

STAYING POWER

The largest study to evaluate the oral therapy imatinib (Glivec/STI571) in patients with chronic myeloid leukaemia (CML) reported a survival rate of nearly 90% after 5 years of treatment.

Five-year follow-up data from the International Randomized Interferon versus STI571 (IRIS) trial were presented at the American Society of Clinical Oncology annual meeting. IRIS enrolled 1,106 newly diagnosed Philadelphia-chromosome-positive CML patients. Of the 553 patients randomized to imatinib rather than standard therapy, 69% remain on imatinib and, of those, overall survival is 89% and disease-specific survival is 95% after 5 years.

"This trend, if it holds, coupled with the low risk of relapse, means that the possibility of long-term survival with CML is increasingly likely," said Brian Druker, the lead author of the study at Oregon Health and Science University (http://www.reuters.com, 3 June 2006).

Furthermore, data from the study also showed that the percentage of patients with a complete cytogenetic response actually increased from 69% to 87% between the first and fifth years of treatment. "Very few oncology medicines offer patients the opportunity to achieve better outcomes the longer they take the therapy," said David Epstein, of Novartis Oncology (http://www.novartis.com, 3 June 2006).

Although imatinib has been heralded as a 'life saver' by patients (http://news.bbc.co.uk, 6 June 2006), Druker, who helped develop imatinib, pointed out that even imatinib has its limits and is not a cure for CML. Over the 5 years of treatment in IRIS, approximately 18% of imatinib-treated patients experienced some form of disease progression, and 5% discontinued therapy because of adverse effects. "People have to remain on therapy and remain on it for the long term," said Druker (http://www.medpagetoday.com, 5 June 2006).

Sarah Seton-Rogers

TUMOUR METABOLISM

Shifting the balance

Upregulation of glycolysis, the anaerobic breakdown of glucose to produce ATP, occurs in almost every tumour. Paul Hwang and colleagues propose that such a widespread metabolic alteration must be stimulated by a pathway with similarly widespread alterations in cancer, and found that *TP53*, one of the most commonly mutated genes in human cancers, can alter the balance between glycolysis and aerobic respiration in tumour cells.

Cancer cells seem to increase glycolysis even in the presence of ample oxygen (a process termed the 'Warburg effect'), and glycolysis seems to correlate with tumour aggressiveness, indicating that it might be crucial in the evolution of malignancies. Hwang and colleagues set out to determine if loss of the tumour suppressor p53 could increase the level of glycolysis and reduce aerobic respiration.

The authors first showed that mitochondria prepared from mice with *Trp53* disruption showed significantly lower levels of oxygen consumption than *Trp53* wild-type mice, and they observed a similar reduction in HCT116 human colon

> "*TP53* ... can alter the balance between glycolysis and aerobic respiration in tumour cells."

DNA VACCINES

Provoking a response

The inhibition of angiogenesis to reduce tumour progression has shown promise, but the short half-life and high production costs of endogenous angiogenesis inhibitors, such as angiostatin, have hindered clinical development. Lars Holmgren *et al.* now report that vaccination with DNA that encodes the angiostatin receptor, angiomotin, overcomes these problems and those of developing active immunotherapies by breaking immune tolerance and provoking an immune response against angiogenesis. In addition, the angiomotin vaccine inhibited tumour progression in mice when given in combination with a tumour-cell-targeted DNA vaccine.

The authors used cDNA that encodes the human p80 isoform of angiomotin inserted into a plasmid vector (pcDNA3–Amot), and showed that transfection into the cervical cancer cell line, HeLa, led to expression of the angiomotin protein. Intramuscular injection and electroporation with pcDNA3–Amot into mice that were then challenged by the injection of mouse breast cancer cells led to the prolonged suppression of tumour growth compared with the injection of a control vector.

> "This approach to inhibiting angiogenesis overcomes problems commonly seen with other angiogenesis inhibitors and immunotherapies."

Next, the BALB-NeuT transgenic breast cancer mouse model (which is positive for rat epidermal-growth-factor receptor 2 (ERBB2, also known as HER2)) was used to investigate the ability of angiomotin to inhibit the angiogenic switch and tumour progression. The mice were vaccinated either before or after the onset of tumour angiogenesis, and although no effect on tumour progression was seen, vaccination reduced tumour angiogenesis by over 60%. Importantly, pcDNA3–Amot vaccination did not negatively affect the vasculature of the surrounding stroma or the vessels

cancer cells with targeted *TP53* disruption. Although oxygen consumption was decreased, the amount of ATP produced by HCT116 cells was the same regardless of p53 status, which indicates that the p53-deficient cells preferentially used glycolysis rather than aerobic respiration. Furthermore, the cells with *TP53* disruption produced significantly higher levels of lactate, the primary by-product of glycolysis.

How does p53 affect mitochondrial respiration? The authors examined a serial analysis of gene expression (SAGE) database from HCT116 cells with and without *TP53* disruption, and found that the induction of *SCO2* (synthesis of cytochrome *c* oxidase 2) was ninefold greater in cells with intact p53. SCO2 regulates the cytochrome *c* oxidase complex, which has a crucial role in aerobic respiration in mitochondria. SCO2 protein levels were reduced in both HCT116 cells and mouse mitochondria that lacked p53, and expression of SCO2 increased oxygen consumption in p53-deficient HCT116 cells and two other colon cancer cell lines with mutations in *TP53*. The authors confirmed these data by showing that parental HCT116 cells with either small interfering RNA knock down of p53 expression or disruption of the *SCO2* allele phenocopied the p53-deficient HCT116 cells.

Can p53 directly activate *SCO2* transcription? Inducible expression of p53 increased *SCO2* mRNA levels in 3–18 hours, which indicates direct activation. Furthermore, the authors identified a p53 DNA-binding consensus sequence in intron 1 of *SCO2* that was sufficient to induce luciferase reporter expression by p53.

Although this model still needs to be confirmed in human tumours, Hwang and colleagues conclude that the new function of p53 as a direct regulator of aerobic respiration has significant implications for understanding human cancers.

Sarah Seton-Rogers

ORIGINAL RESEARCH PAPER Matoba, S. *et al.* p53 regulates mitochondrial respiration. *Science* 25 May 2006 (doi: 10.1126/science.1126863)
FURTHER READING Gatenby, R. A. & Gillies, R. J. Why do cancers have high aerobic glycolysis? *Nature Rev. Cancer* **4**, 891–899 (2004)

in mice retinas. When pcDNA3–Amot vaccination was combined with a DNA vaccine against ERBB2, 80% of treated mice were tumour free for more than 70 weeks — the ERBB2 vaccination alone delayed tumour growth but progression resumed.

So, what is the mechanism of the anti-angiogenic effect of pcDNA3–Amot? The anti-tumour effect was abrogated in mice that were treated with anti-CD4 antibodies to deplete $CD4^+$ T cells. Furthermore, tumour growth was not inhibited when mice that lacked B cells (which produce antibodies) and antibody μ-chains were vaccinated. Sera harvested from vaccinated mice contained antibodies against angiomotin. Purified immunoglobulin completely blocked migration stimulated by basic fibroblast growth factor or vascular endothelial growth factor in angiomotin-transfected mouse aortic endothelial cells. These results confirm that production of anti-angiomotin antibodies is key to the anti-angiogenic effect of pcDNA3–Amot.

This approach to inhibiting angiogenesis overcomes problems commonly seen with other angiogenesis inhibitors and immunotherapies. Further investigation of angiomotin DNA vaccination, or anti-angiomotin antibodies, in combination with a tumour-targeted agent is warranted.

Ezzie Hutchinson

ORIGINAL RESEARCH PAPER Holmgren, L. *et al.* A DNA vaccine targeting angiomotin inhibits angiogenesis and suppresses tumour growth. *Proc. Natl Acad. Sci. USA* **103**, 9208–9213 (2006)

IN BRIEF

EPIGENETICS

Epigenetic inactivation of the premature aging Werner syndrome gene in human cancer

Agrelo, R. *et al. Proc. Natl Acad. Sci. USA* **103**, 8822–8827 (2006)

Werner syndrome is an inherited disorder caused by loss-of-function mutations in WRN, and is characterized by premature ageing, genomic instability and increased cancer incidence. Now, Agrelo et al. show that WRN expression is disrupted by promoter hypermethylation in human cancer cells from individuals without Werner syndrome. Epigenetic inactivation of WRN leads to increased chromosomal instability in various primary tumours and, in colorectal tumours, is a predictor of response to the chemotherapeutic drug irinotecan.

ANGIOGENESIS

Semaphorin 4D provides a link between axon guidance processes and tumor-induced angiogenesis

Basile, J. R. *et al. Proc. Natl Acad. Sci. USA* **103**, 9017–9022 (2006)

Tumour angiogenesis is crucial to tumour progression and metastasis. Basile et al. show that the axon-guidance molecule semaphorin 4D (SEMA4D) is highly expressed at the cell surface of invasive epithelial cells in head and neck squamous-cell carcinomas (HNSCCs). SEMA4D release by HNSCC cells induces endothelial cell migration in vitro, and RNA inhibition of SEMA4D reduces the size and vascularity of HNSCC tumour xenografts. SEMA4D might be a good therapeutic target for solid tumour treatment.

PHARMACOGENOMICS

Serine protease HtrA1 modulates chemotherapy-induced cytotoxicity

Chien, J. *et al. J. Clin. Invest.* 8 June 2006 (doi:10.1172/JCI27698)

The expression of the serine protease HTRA1 is often decreased in ovarian cancer. Chien et al. show that decreased expression of HTRA1 attenuates cisplatin cytotoxicity, and re-expression of HTRA1 sensitizes ovarian cells to cisplatin. Cisplatin increases the expression of HTRA1, leading to autoproteolysis and activation of HTRA1, which induces cell death in a serine-protease-dependent manner. HTRA1 expression was also shown to predict the response of ovarian and gastric tumours to treatment with cisplatin in vivo.

GENOMIC INSTABILITY

The retroviral oncoprotein Tax targets the coiled-coil centrosomal protein TAX1BP2 to induce centrosome overduplication.

Ching, Y.-P. *et al. Nature Cell Biol.* 11 June 2006 (doi: 10.1038/ncb1432)

Human T-cell leukaemia virus type I (HTLV-I) is a retrovirus that is associated with adult T-cell leukaemia (ATL). ATL cells are aneuploid, so Yick-Pang Ching and colleagues investigated whether this aneuploidy is caused by supernumerary centrosomes, a known mechanism for inducing genomic instability. They found that the HTLV-I oncoprotein Tax can localize to the centrosome and bind to TAX1BP2, a protein that can inhibit centrosome duplication. So, HTLV-I might induce genomic instability through the interaction of Tax with TAX1BP2.