IN THE NEWS

Ready for prime-time?
A proteomic test designed to detect ovarian cancer at its earliest stages has raised concerns about the best way to regulate the efficacy and proper use of the latest high-throughput diagnostic technologies.

OvaCheck, which uses mass-spectrometry analysis of blood samples to identify patients with ovarian cancer, is based on a study by Petrocoin *et al*. (*The Lancet*, 16 February 2002). At issue is the marketing by one of the companies licensed to conduct the test before its validation and approval by the US Food and Drug Administration (FDA). "The results have not been reproduced, and the test needs to be controlled for potentially confounding factors …" said Eleftherios P. Diamandis, University of Toronto (L. Wagner, *JNCI Cancer Spectrum*, 7 April 2004).

It is not clear, however, which government agency should regulate these new diagnostics, as the FDA has never before evaluated a multiplex test in which more than one protein is used as a marker. According to FDA official Steven Gutman, it is not clear if the test is "subject to regulation by [the Centers for Medicare and Medicaid Services], under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), or whether it may also require premarket review by the FDA" (L. Wagner, *JNCI Cancer Spectrum,* 7 April 2004).

The US government will need to quickly find a balance between the interests of patients, who want access to the latest diagnostics, and the careful regulation of these assays, as more become available. A gene-expression-profile test called OncotypeDX, developed by a company called Genomic Health to identify women who are likely to undergo breast cancer recurrence, has already appeared on the market with CLIA approval, but without FDA review.

Kristine Novak

THERAPEUTICS

Staying on target

Although anti-angiogenic agents hold promise as cancer therapies, one challenge of this approach is to disrupt the tumour vasculature without affecting normal blood vessels. In the April issue of *The Journal of Clinical Investigation*, Greenberger *et al.* describe a gene-therapy approach that specifically targets the endothelial cells of the growing tumour vasculature.

Tumour blood vessels make good therapeutic targets, not only because the tumour depends on their delivery of oxygen and nutrients for growth, but also because the vasculature comprises endothelial cells that are more genetically stable and, therefore, less prone to drug resistance. But how does one destroy the blood vessels of a tumour without affecting those of normal tissues? Greenberger and colleagues created an adenoviral vector that expressed a chimeric death receptor — composed of elements of the FAS receptor and tumour-necrosis factor receptor 1 (TNFR1) — specifically in vascular endothelial cells. This receptor was designed to activate the FAS-induced apoptotic pathway following binding to TNF-α, which is abundant in the tumour microenvironment. Furthermore, the gene encoding this receptor was placed under transcriptional control of the modified endothelial-cell-specific pre-proendothelin-1 (*PPE-1*) promoter. PPE-1 is a vasoconstrictor and smooth muscle cell mitogen that is synthesized by endothelial cells. The *PPE-1* promoter contains a hypoxia-responsive element that increases gene expression only under hypoxic conditions, such as in the tumour microenvironment. For extra specificity, Greenberger *et al.* engineered their therapeutic vector to contain three copies of the endothelial-cell regulatory elements of this promoter.

The vector lived up to expectations — it induced gene expression only in angiogenic vessels, and apoptosis only in cultured endothelial cells in the presence of TNF-α. But did it work in tumours? The authors injected the chimeric FAS-expressing vector into the tail vein of mice carrying Lewis lung carcinomas and observed that transcription of the gene encoding the chimeric FAS receptor was restricted to the tumour-bearing lung. Furthermore, the treatment resulted in a 56% decrease in the weight of the lung metastases, compared with controls. Lung surfaces of mice treated with the therapeutic vector were free of tumours or partly covered by small, underdeveloped metastases, whereas the lungs of control animals were almost completely replaced by tumour tissue. The FAS chimeric vector was also effective in slowing tumour growth in mice with pre-existing B16 melanomas, and the authors showed that these tumours succumbed to necrosis.

Histological analysis revealed that the tumour vasculature was specifically targeted in mice that received the therapeutic vector — tumour blood vessels were damaged and had lost their endothelial layer. Antivascular effects were not observed, however, in normal, non-angiogenic tissues, and no humoral immune response against the transgene product was observed. Importantly, expression of the chimeric receptor did not cause liver damage in mice, which was a concern because FAS-ligand administration has been previously shown to destroy hepatocytes. The authors believe that the chimeric features of the receptor allowed TNF-α to only activate FAS signalling and apoptosis within the tumour microenvironment.

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References and links

ORIGINAL RESEARCH PAPER Greenberger, S. *et al.* Transcription-controlled gene therapy against tumor angiogenesis. *J. Clin. Invest.* **113**, 1017–1024 (2004)

FURTHER READING Ashkenazi, A. Targeting death and decoy receptors of the tumour-necrosis factor superfamily. *Nature Rev. Cancer* **2** 420–430 (2002)