TRIAL WATCH

Cytokine gene therapy

A modified adenoviral vector designed to express melanoma differentiation-associated 7 gene (*MDA7*) has been shown to destroy up to 70% of tumour cells in patients with advanced carcinoma. The results of a Phase I dose-escalation study of this vector, named INGN-241, were reported by Sunil Chada *et al.* (from Introgen Therapeutics Inc., Houston, Texas), at the annual meeting of the American Society of Gene Therapy in June. The study investigated the effects of a single intratumoral injection of INGN-241 in patients with advanced carcinoma who had a surgically resectable lesion. At specific times after injection, the lesions were excised, sectioned and analysed for vector distribution, MDA7 protein levels and apoptosis induction. A total of 80% of the tumour cells expressed the MDA7 protein. MDA7 and vector DNA could also be detected in sections up to 1 cm from the point of injection. INGN-241 was reported to have few toxic side effects, causing only pain at the injection site, transient low-grade fever and mild flu-like symptoms.

MDA7 is an immune activator that is produced by natural-killer cells and B cells, and that has been classified as interleukin-24 (IL-24) — a member of the IL-10 family. Previous results have shown that adenoviral transfer of *MDA7* induces apoptosis in a wide range of tumour cells — including lung, breast, colon, prostate and melanoma — without killing normal cells. INGN-241 is also being tested in combination with the chemotherapeutic agents doxorubicin, taxotere, tamoxifen and trastuzumab (Herceptin) to treat breast cancer.

ORIGINAL RESEARCH PAPER Chada, S. *et al*. A Phase I dose-escalation pharmacokinetic and pharmacodynamic study of Ad-mda7 (INGN-241) in patients with advanced carcinoma. The 5th Annual Meeting of the American Society of Gene Therapy, Boston, Massachusetts, 5–9 June 2002. Abstract No. 814.

WEB SITE http://www.apnet.com/www/journal/asgt/814.htm

Testing a new receptor tyrosine kinase inhibitor

A Phase I clinical trial of a novel small molecule designed to inhibit signalling by the fms-like tyrosine kinase-3 (FLT3) receptor tyrosine kinase has been initiated in patients with acute myeloid leukaemia (AML). The open-label study of the drug, MLN-518, is being coordinated by Millenium Pharmaceuticals, Inc. to assess its tolerability, safety and pharmacokinetic properties. The study is being conducted at five US sites in about 40 AML patients who have relapsed within 12 months of therapy, in newly diagnosed patients with AML or in patients who are not candidates for conventional chemotherapy. AML represents 90% of all adult acute leukaemias, and has an overall five-year survival rate of only 14%. Approximately 30% of AML patients possess an internal tandem duplication in the gene that encodes FLT3, and this defect has been implicated in the growth and survival of leukaemic cells. AML patients who carry this *FLT3* mutation generally have poor prognoses and few treatment options.

FLT3 binds the cytokine FLT3 ligand (FLT3L), and signalling by this receptor is involved in the early stages of haematopoiesis. FLT3 is expressed by CD34+ fetal liver and bone-marrow stem cells, pre-B cells, pro-B cells, immature thymocytes and monocytes, as well as AML and B-cell precursor acute lymphoblastic leukemia blast cells. In pre-clinical studies, MLN-518 selectively killed human AML cells that express the FLT3 receptor. The small molecule has also been shown to inhibit the platelet-derived growth-factor receptor and c-KIT tyrosine kinases, so it might also be used to treat other haematological malignancies or solid tumours. Millenium Pharmaceuticals are also searching for biomarkers that will identify patients who are most likely to respond to MLN-518 treatment.

WEB SITE http://www.mlnm.com/news/2002/05-29—0.html

METASTASIS

On the edge

Metastasis of cancer cells in humans occurs mainly via the blood and lymphatic systems. Whereas the role of angiogenesis in cancer metastasis has been well studied, the mechanisms of escape of tumour cells — from the primary tumour to distant sites, via the lymphatic system — are less well understood. In the 7 June issue of *Science*, Timothy Padera *et al.* discuss the contribution of the lymphatic system to tumour metastases in mice, focusing on the differences between lymphatics within the tumour and at the tumour edge. The authors used cutaneous melanoma and fibrosarcoma xenografts that were engineered to overexpress VEGFC, a member of the vascular endothelial growth factor (VEGF) family that is involved in stimulating the formation of lymphatic vessels. They also studied tumours in patients with lung cancer. Unlike previous studies, which have concentrated on using either molecular markers or functional assays to investigate lymphangiogenesis, this research combined the two approaches.

Although the expression of VEGFC in the experimental tumours correlated with the incidence of lymph-node metastases and increased staining of lymphatic markers in and around the tumours, functional lymphatic vessels were not found within the tumours. However, these VEGFC-overexpressing tumours all had functional lymphatic vessels in the tumour margin, which is defined as <100 μm from the tumour edge. The vessels in the tumour margins were dilated, and Padera *et al.* propose that this explains the increase in lymph-node metastases that arise from these tumours. The authors conclude that functional lymphatics in the tumour margin are therefore sufficient for lymphatic metastasis.

To further support their claim, Padera *et al.* studied a group of 22 patients with lung cancer. The patients had interstitial hypertension, greatly reduced lymphatic function in their tumours and almost no intratumoral lymphatic staining. However, nearly half the patients had metastases in regional lymph nodes, confirming the observations in mice that lymphatic vessels in the tumour margin are sufficient for tumour spread.

So how can these findings help treatment of patients with cancer? The authors suggest that the tumour margins should be treated aggressively by local treatment, such as surgery and radiation, to combat lymphatic dissemination. In addition, the role of VEGFC in lymphangiogenesis makes it a potential target for combatting lymphatic metastasis.

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References and links

ORIGINAL RESEARCH PAPER Padera, T. P. *et al*. Lymphatic metastasis in the absence of functional intratumour lymphatics. *Science* **296**, 1883–1886 (2002)

FURTHER READING Gershenwald, J. E. & Fidler, I. J. Targeting lymphatic metastasis. *Science* **296**, 1811–1812 (2002) | Jain, R. K. & Fenton, B. T. Intratumoral lymphatic vessels: a case of mistaken identity or malfunction? *J. Natl Cancer Inst*. **94**, 417–421 (2002)

WEB SITE

Rakesh Jain's lab: http://steele.mgh.harvard.edu/home.html