surrounding the safety of gene therapy, it is also important to develop a suitable and convenient delivery system,' he says. Catheter delivery is one option, targeted delivery by identifying key markers on target cells is another. Currently, in addition to investigating possible vectors that could be used to replace direct injection, Metzger and his team are developing transgenic mice that express parvalbumin in heart muscle to carry out dose–response studies. 'This will enable us to investigate what side-effects might result from over-expression,' says Metzger.

Poole-Wilson also warns that it will be important to determine whether the use of parvalbumin is energy consuming. 'Once the calcium has been attached to parvalbumin, it must then be released and either temporarily taken up by the SR or excreted by the cell. Both these processes consume energy and it will be interesting to see how much energy is required in the human heart, which has a slightly different calcium release system compared with the rat heart,' he says. Metzger agrees that energetics is an important issue, 'particularly because the failing heart is thought to be energetically compromised.'

Metzger and colleagues are also moving into larger mammalian models; studies of gene transfer in dogs are under way, and *in vitro* studies using myocytes from heart failure patients who undergo heart replacement are also planned. If a safe, high-efficiency vector can be found, and if stable and long-lived expression of parvalbumin can be achieved, human trials could be possible, but this could be a way off yet. Poole-Wilson agrees but emphasizes that this study is an impressive proof-of-principle that could have substantial application. 'There is currently a race between the clinical application of pumping devices, cell transplantation and gene therapy. Seeing how these three approaches to heart failure will fit into the current therapeutic armatarium should be interesting,' he concludes.

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Vaccine stops blood supply

Sharon Dorrell, Freelance writer

Researchers at EntreMed (Rockville, MD, USA) believe they can arrest tumour growth with an experimental vaccine designed to block angiogenesis, the process by which tumours create their own blood supply (see Box 1). Stacy Plum and colleagues vaccinated mice with a 42-amino acid peptide derived from basic fibroblast growth factor (FGF-2)[1], one of the factors that stimulates angiogenesis[1]. Vaccination inhibited new blood vessel formation and protected mice against experimental melanoma and lung carcinoma metastasis (Fig. 1).

Several approaches to blocking angiogenesis are currently under investigation. These include inhibitors of vascular endothelial growth factors (VEGFs) and inhibitors of the degradative enzymes involved in the early stages of angiogenesis[2]. However, the scientists at Entremed believe their technique is unique. Anne Fortier (Senior Director, Preclinical Sciences, EntreMed) believes that no one has yet attempted a vaccine approach that targets factors other than cancer antigens. 'This approach will enable us to target both processes: prevention of new tumour development and

Box 1. Angiogenesis

Angiogenesis is key to the success of the invasion of the body by tumours. Without an adequate blood supply, tumours cannot grow beyond a few millimetres in size and might only survive as thin layers of cells that cause no symptoms[2,3]. A rich blood supply, however, enables them to grow and shed their cells into the bloodstream, thus giving them access to other tissues where secondary tumours can form.

The process begins with the stimulation of vascular endothelial cells to degrade the local basement membrane and migrate to form new capillary branches from the parent blood vessel[3]. This process requires several degradative enzymes as well as vascular and fibroblast growth factors to build the new blood vessels. These factors include FGF-2, other fibroblast growth factors, vascular endothelial growth factors, tumour necrosis factor-α, platelet-derived growth factor, interleukin-8, as well as other peptide and non-peptide factors[2]. By inhibiting this process and cutting off tumour blood supply, it is possible to kill tumour cells and arrest tumour growth and spread[2].

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restriction of growth and spread of tumours, as well as improving the potential effectiveness of other anticancer treatments,' she adds.

FGF-2 fragments

FGF-2 is a single-chain polypeptide that acts as an angiogenic stimulator. Previous research has shown that monoclonal antibodies against FGF-2 block FGF-2-stimulated angiogenesis[1]. FGF-2 also increases metastatic potential in tumour cells, and levels of the angiogenic factor are inversely correlated with survival in patients with renal, breast, endometrial, prostate or colorectal cancer.

Under normal conditions, FGF-2 works in conjunction with other stimulators (such as VEGFs and interleukin-8) and angiogenesis inhibitors (such as angiostatin and endostatin proteins) to maintain a homeostatic balance. However, the presence of tumour cells shifts the balance in favour of new blood vessel growth by up-regulating angiogenic stimulation and down-regulating angiogenic inhibition[1–3].

The vaccine

Proliferation and migration of endothelial cells in response to FGF-2 is mediated by a two-component receptor system that binds two portions of the FGF-2 peptide – the heparin-binding and receptor-binding domains. Plum and colleagues synthesized two peptides identical to these domains. They then produced two liposomal vaccines that also contained lipid A to stimulate an immune response[1]. However, mice vaccinated with the receptor-binding domain fragment showed little or no immunoreactivity whereas those vaccinated with the heparin-binding domain produced a strong response[1]. The heparin-binding domain vaccine also inhibited experimental angiogenesis in vaccinated mice and prevented melanoma and lung carcinoma metastasis.

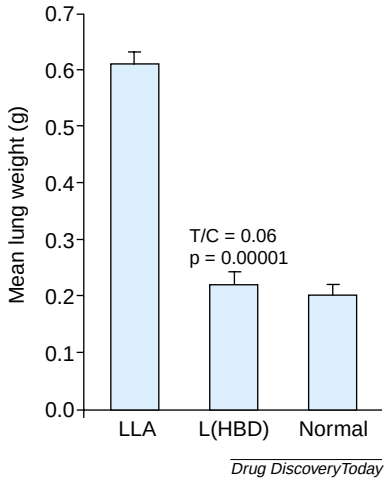

Figure 1. Inhibition of Lewis lung carcinoma-low metastatic experimental metastases in five mice vaccinated with either the new vaccine [liposomal heparin binding domain – L(HBD)] or liposomal lipid A (LLA; control). The 'normal' mice were neither vaccinated nor challenged with the lung cancer cells. After 17 days, L(HBD) inhibited lung metastases by 95%[1]. [Reproduced with permission of Entremed.]

Potential problems

As well as angiogenesis, FGF-2 is also involved in embryonic development, wound healing and other processes that could, in theory, be adversely affected by the new vaccine. The researchers are therefore cautious about its long-term effects. Fortier states, however, that future research articles will address the effects of the vaccine on these processes. In the meantime, the vaccine is being developed with a view to future clinical studies.

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Genome sequences reveal key genetic element in PD

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Researchers from the National Human Genome Research Institute (NHGRI; Bethesda, MD, USA) have uncovered a novel genetic element that could be crucially involved in Parkinson's disease (PD). This element is involved in transcriptional control of levels of α-synuclein, believed to be important in both inherited and non-inherited forms of PD[1]. They hope that increased understanding of the control of the expression of this protein could lead to the development of novel therapies for PD.

α-Synuclein

PD results from the loss of dopaminergic neurons in the substantia nigra and other regions of the brain. In their efforts to find the cause of PD, researchers have been focusing on the mysterious protein α-synuclein, a presynaptic nerve terminal

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