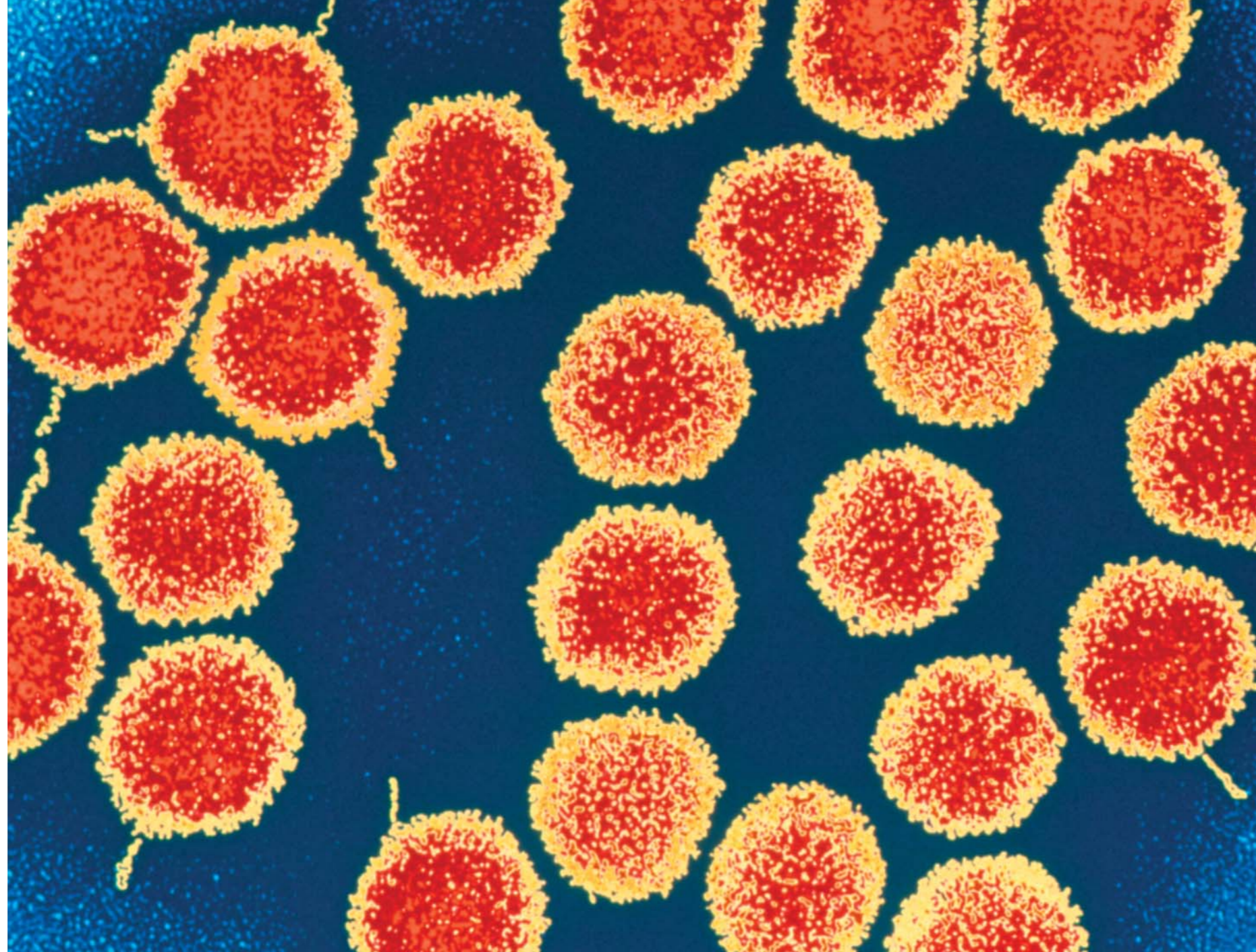


Gene therapy using viruses, commonly thought of only as agents of disease, offers great promise for the treatment of cancer as **Moira Brown** explains.



◀ Coloured transmission electron micrograph of a section through recombinant adenoviruses used in gene therapy. J.C. Revy/Science Photo Library

Killer into cure – oncolytic viruses

Over the last few years, a new word has crept into the vocabulary of virologists – virotherapy – the use of viruses for therapeutic purposes. In general, the word has been applied in the field of gene therapy and in the use of viruses for the treatment of cancer. This article concentrates on the latter and more specifically on oncolytic viruses.

Oncolysis describes the lysis of tumour cells by harnessing the innate ability of viruses to multiply rapidly and produce large quantities of progeny virus which results in cell death. Selectivity is achieved by modifying the virus in such a way that its replication potential is specific for tumour

cells and not for normal cells. Genetic manipulation and an intimate knowledge of virus replication strategies coupled to an understanding of at least some of the pathways involved in tumorigenesis has allowed us to do this with relative ease. Knocking out specific virulence factors is all that is required in the case of several viruses.

Early findings

The concept of viruses as therapeutic agents is not a new one. At the beginning of the last century, there were reports of cancer patients in remission from tumour progression after bouts of 'fortuitous' virus infections, such as remission of Hodgkin's lymphoma following measles virus infection. Planned human trials using viruses

to treat cancer were initiated as early as the 1950s, but abandoned due to lack of selectivity and poor efficacy data. A new era dawned in the early 1990s with the report of a herpes simplex virus (HSV) engineered to replicate specifically in tumours. Since then, variants of HSV, adenovirus, *Vaccinia* virus, *Poliovirus*, influenza virus, reovirus, *Newcastle disease virus* and vesicular stomatitis virus have all been shown to have oncolytic potential in a range of tumour models and some of these viruses have been safely and successfully used in the clinic.

Approaches to therapy

Selective replication strategies have included inactivation of virulence determinants, e.g. removal of expres-

sion of ICP34.5 in HSV and the targeting of specific pathways defective in tumours, such as pRb and p53 (E1A and E1B deletion in adenovirus) and the activated Ras pathways (reovirus). These approaches have been shown to be effective in achieving tumour regression and/or eradication and prolonging survival times of tumour-bearing animals. A range of tumour models (mouse/mouse and human/mouse) have been used – glioma (a cancer of the brain), melanoma, mesothelioma (cancer of membranes lining the body cavities), ovarian carcinoma, mammary carcinoma and non-small cell lung carcinoma are just a few of the tumours which have been shown to be susceptible to oncolytic viral therapy.

Viruses can be easily manipulated to act as vectors for exogenous genes and it would be good to think that several forms of anti-cancer treatment could be incorporated into one 'magic bullet'

Viruses on trial

By the mid-1990s, clinical trials using oncolytic adenovirus and oncolytic HSV were underway. In the UK these trials required approval by the Department of Health, Gene Therapy Advisory Committee (GTAC) and in the USA, the equivalent committee of the Food and Drug Administration (FDA). It was no mean feat to persuade these authorities that directly injecting HSV into someone's brain should be allowed. HSV is after all a neurotropic virus which remains latent in the peripheral nervous system throughout life and on infection of the brain causes a fulminant encephalitis which, before the advent of acyclovir, was life-threatening. Those of us involved at the time had to be very convinced of the science behind the approach and also had to be either fairly brave or foolhardy! Lives could have been at risk not to say careers! Gladly, up until now all has gone well. I am unaware of any serious adverse events arising in patients from administration of oncolytic viral therapy. On the contrary these treatments have been remarkably free of side effects.

There are major ethical considerations to be taken into account in any clinical trial and one cannot take the cavalier approach of assuming that because patients have cancer, they have nothing to lose. Phase I and II clinical trials using either oncolytic adenovirus or HSV have successfully taken place in a range of cancers. In 2004, permission was granted by the European Medicines Agency (EMA), GTAC and the Medicines and Healthcare Products Regulatory Agency (MHRA) for the most advanced trial to date using an oncolytic virus. The trial, using HSV1716 in the treatment of

patients with recurrent glioma, is a pivotal efficacy trial which could lead directly to a licence and marketing approval on the basis of satisfactory results.

Future challenges

Exciting times are ahead for this pioneering approach to cancer therapy. We need to show efficacy and we need to face the challenges of this type of therapy. These challenges include efficient delivery – a single direct injection into tumour is not efficient and there is a major effort now going on to find ways to deliver virus systemically and to target specific tumour types. We need to know if the immune surveillance mechanisms which most of us have to common viruses affect efficacy and if so, can they be circumvented. Viruses can be easily manipulated to act as vectors for exogenous genes and it would be good to think that several forms of anti-cancer treatment could be incorporated into one 'magic bullet'. Control and management is the current approach to cancer treatment. How much better it would be for the patient if one or more combinations of oncolytic virus

therapy, targeted chemotherapy, radiotherapy, antibody therapy and anti-sense therapy could be delivered as a single entity. These are the goals which we hope to achieve, but first of all we must show that oncolytic virus therapy is effective, easy to use and economically viable. The use of oncolytic viruses for the treatment of cancer is an excellent example of translation of basic laboratory findings into the clinic and exemplifies what medical research should be – use of knowledge and expertise to hopefully improve the lot of mankind.

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▼ Brain scans from a patient involved in the third HSV1716 trial. In each case the four scans on the left-hand side are MRI and the two on the right are SPECT (the bright area in the bottom right-hand corner of the SPECT scans is active tumour). (a) Pre-injection of HSV1716; (b) 6 weeks post-injection; (c) 22 months post-injection. Moira Brown/Jennifer Stewart

