

HARNESSING VIRUSES AS CANCER THERAPEUTICS

In the past a great deal of research has focused on the role of certain types of viruses in causing cancers. However, in recent years the tables have been turned and viruses are now being enlisted as potential cancer treatments.



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Oncolytic viruses

In the last 50 years, there have been a number of anecdotal reports of viral infections causing disease remission in patients with advanced cancers. In the last decade, these reports have been supplemented by data indicating the potential anti-tumour effect of a number of viruses that selectively destroy cancer cells. These so-called oncolytic viruses fall into two groups:

- (I) Naturally-occurring viruses that have evolved to grow preferentially in cells, such as cancer cells, that have acquired specific genetic defects;
- (II) Viruses that have been genetically engineered to be able to grow selectively in cancer cells.

■ We are currently conducting laboratory and clinical trials of viruses from each of these classes at The Institute of Cancer Research and The Royal Marsden. ■

Phase I trials

In collaboration with Dr Johann de Bono of The Royal Marsden's Drug Development Unit and The Institute's Section of Medicine, and colleagues at St George's Hospital, we have completed a Phase I trial of a type of oncolytic virus (reovirus) that kills cancer cells with abnormalities in the Ras signalling pathway (see Figure 1). This work has confirmed the ability of reovirus to target and grow in human tumours after intravenous injections, but has highlighted the effect of the immune system in neutralising circulating virus. As a direct result of this work, a series of Phase I studies of reovirus in combination with

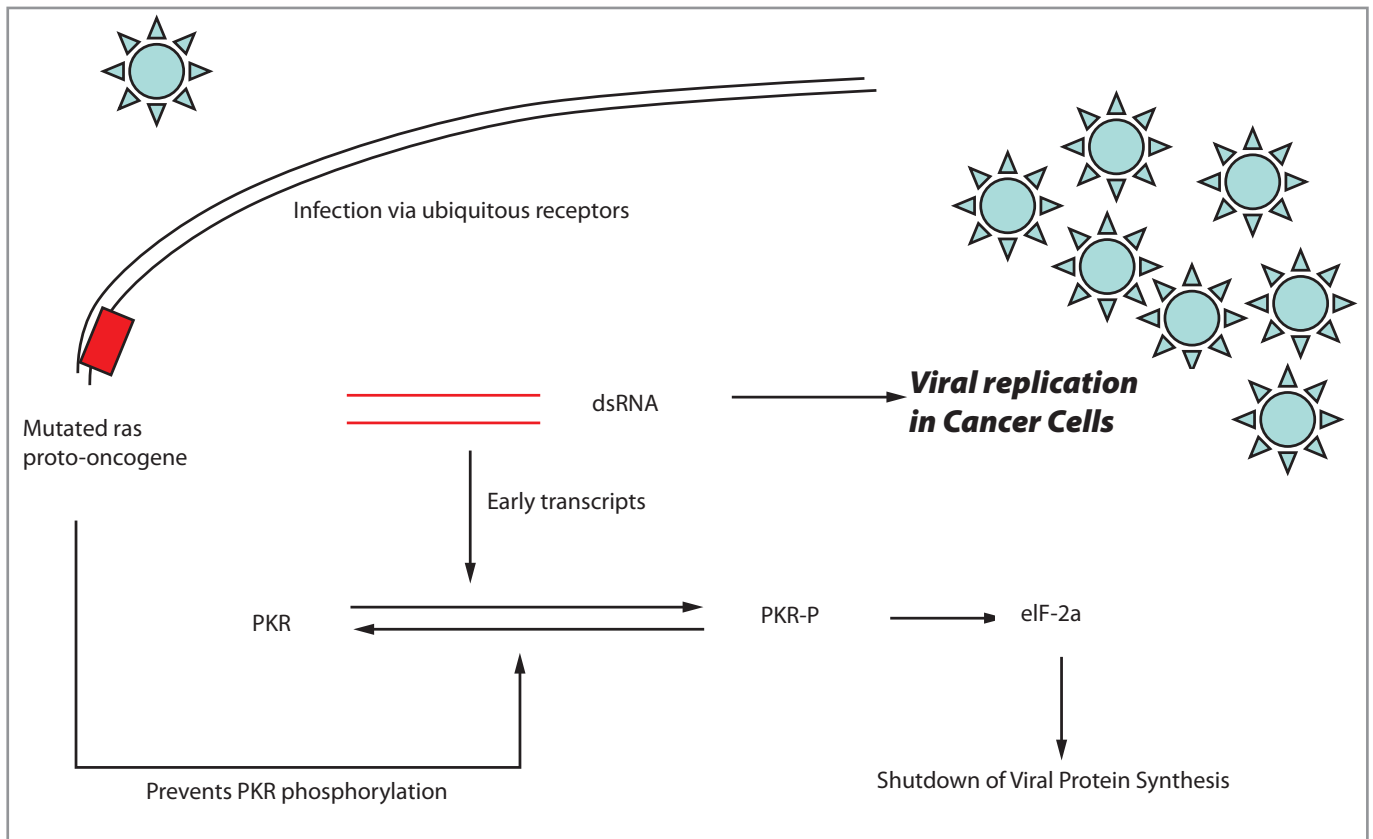


Figure 1: Reovirus infects a wide variety of cells. In normal cells, the presence of viral double-stranded RNA (dsRNA) triggers activation of the PKR defence mechanism that stops the virus replicating. In cancer cells with abnormalities in the Ras signalling pathway, the PKR pathway does not function and viral replication can proceed and result in cell death.

cytotoxic and immunomodulatory drugs will be opening to recruitment in the first half of 2007. These trials have been designed to include patients with tumour types that have been shown to be sensitive to reovirus in laboratory experiments conducted in The Institute.

In a separate Phase I clinical trial, conducted with colleagues at Hammersmith and St George's Hospitals, patients were treated with a genetically engineered oncolytic herpes simplex virus (cold sore virus) that was given by direct injection into the tumour. In addition to being able to kill cancer cells directly, this virus expressed a human protein that stimulated the immune system. The treatment was shown to be safe and promising results were seen in patients with breast cancer, head and neck cancer and melanoma. This trial has prompted two further trials of herpes simplex virus gene therapy at The Royal Marsden. The first of these is a Phase II trial in patients with malignant melanoma and the second involves patients with head and neck cancer who are receiving chemotherapy and radiotherapy.

Radiotherapy and viruses

Radiotherapy is a mainstay of treatment for many common types of cancer. Combinations of radiotherapy and viral therapies present exciting new opportunities to treat cancer. On the one hand, radiation may favourably

alter the effect of the virus on cancer cells and, on the other, the virus may sensitise the cancer cell to the effect of radiation. Laboratory studies at The Institute have confirmed improved rates of tumour cell kill when radiotherapy is combined with reovirus treatment. These results have led to a two-part Phase I study of the combination of radiotherapy and reovirus treatment at The Royal Marsden. Escalating doses of virus and radiation have been shown to be safe and to have an effect against the tumour in some patients.

■ These encouraging results have resulted in the opening of a follow-up multicentre Phase II trial. ■

Laboratory studies performed at The Institute with the herpes simplex virus have demonstrated that this agent is able to enhance the effect of radiation in cancer cells. These data served as the rationale for initiating a Phase I dose-escalation trial of this agent in combination with definitive radical chemoradiotherapy in patients with stage III and IV head and neck cancer (see Figure 2). This study is the first to use genetically engineered oncolytic viruses in the treatment of patients with newly diagnosed head and neck cancer. The dose-escalation cohorts have

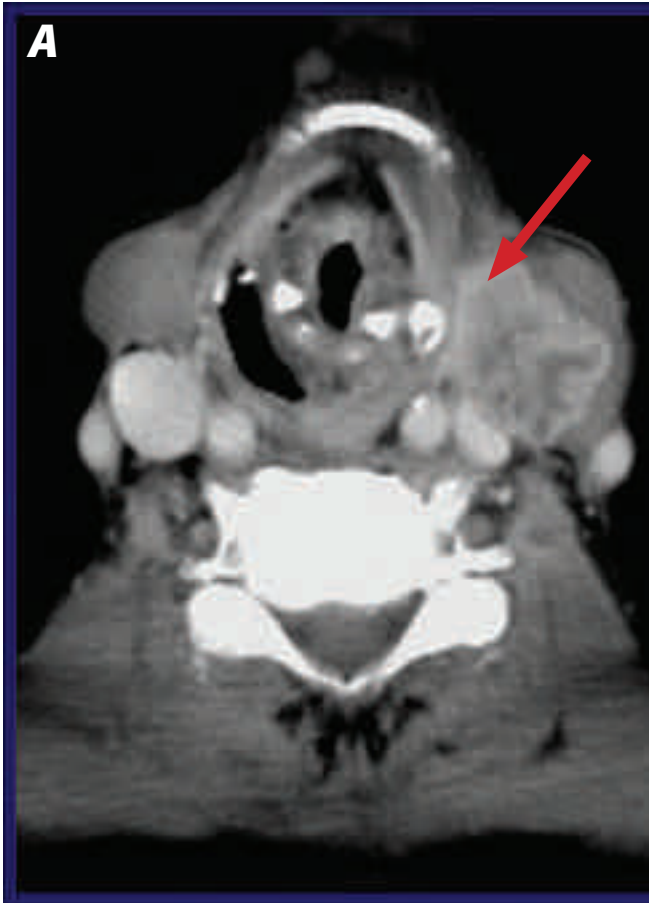


Figure 2: CT scans showing the result of combined chemoradiotherapy and herpes viral gene therapy in a patient with an advanced head and neck cancer. (A) The red arrow in the pre-treatment image shows a large lymph node containing metastatic cancer. (B) This node resolved completely after treatment.

been completed and the treatment has been shown to be safe and tolerable. A further expansion of the trial is currently under way.

GDEPT (Gene directed enzyme prodrug therapy)

My team has established a collaboration with Institute scientists Richard Marais, Professor of Molecular Oncology, and Caroline Springer, Professor of Biological Chemistry, that will result in a three-stage Phase I trial of GDEPT. This approach, which was developed in the Cancer Research UK Centre for Cancer Therapeutics at The Institute, will involve intratumoural injections of an oncolytic adenovirus that manufactures a bacterial enzyme, carboxypeptidase G2, capable of converting a harmless prodrug into a potent chemotherapy drug. The adenovirus has been genetically engineered to ensure that the bacterial protein is expressed selectively within tumour cells.

▣ This study will be the first clinical trial of its kind using GDEPT with an oncolytic virus. ▣

Vaccination against head and neck cancer

A specific type of cancer that affects the back of the nose (undifferentiated cancer of nasopharyngeal type, UCNT) is caused by the Epstein-Barr virus. UCNT is a rare tumour in the UK but extremely common in other parts of the world, including China and the Mediterranean. In partnership with colleagues in Birmingham, we are currently recruiting patients to a Cancer Research UK-sponsored clinical trial in which we are vaccinating patients in remission from UCNT with a genetically modified version of vaccinia virus (the virus used to eradicate smallpox) that expresses parts of two proteins from the Epstein-Barr virus. Patients will receive intradermal injections of the genetically modified virus and the effect of the vaccination schedule on the patients' immune systems is being measured in Professor Alan Rickinson's laboratory at Birmingham University.

NIS and radioiodide treatment

As part of our ongoing efforts to develop new means of exploiting viruses as cancer therapeutics, we have evaluated the use of tumour-selective adenoviruses as a means of concentrating radioactive iodine in cancer

cells. By introducing the *NIS* gene, which is normally responsible for iodine uptake in normal thyroid tissue, we have demonstrated the ability to kill colorectal and head and neck cancer cells in the laboratory. An additional development is the use of this approach alongside standard external beam radiotherapy and specific drugs that sensitise tumour cells to the effects of radioiodine. Using this combination we have been able to demonstrate dramatic evidence of sensitisation of head and neck, lung and colorectal tumour cells to the effects of radioactive iodine. This strategy represents an exciting way of specifically boosting the radiation dose delivered to tumour tissue and will also allow us to investigate the use of very potent radiosensitising drugs that might otherwise be too toxic to use with external radiation alone.

Gene therapy during surgery

The Head and Neck Unit at The Royal Marsden has pioneered the use of a new surgical technique that permits highly concentrated doses of radiation to be delivered to sites of recurrent disease in areas that have previously received full doses of external beam radiotherapy. This technique involves removal of the tumour and adjacent normal tissues and reconstruction of the surgical defect with a piece of tissue (a flap) transplanted from elsewhere on the patient's body. Radioactive catheters are placed at the base of the flap so that high doses of radiation can be delivered to the site from which the tumour was removed. We are currently working on expanding the utility of this technique by assessing our ability to use viruses to turn the flap into a factory that is able to make proteins that can kill cancer cells or improve the immune system's reaction to the cancer. Laboratory studies have shown that this technique has considerable potential for clinical application.

