How has your work evolved over the course of your career?

My surgical experience has challenged me to find new ways to use surgical techniques to deliver chemotherapy to tumours. I was involved in the development and testing of regional chemoperfusions for regionally-confined metastatic tumours that are beyond standard resection options, but still confined to an organ or region of the body. I was then able to use these techniques to deliver biologic agents, and began looking at oncolytic viruses as agents that could be delivered via regional perfusion. This led to my studies with vaccinia virus, and the development of the oncolytic vaccinia virus.

Historically, how has viral therapy been used in the treatment of cancer?

Viruses were first tested as non-replicating agents to express tumour antigens (molecules the immune system is capable of recognising), or to mix with tumour cells and create an oncolysate (an agent that destroys tumour cells) in vitro, and deliver this to patients as a vaccine.

As the concept of gene therapy became popular in the 1990s, it was recognised that the best utility may be to consider replicating viruses as a more efficient means of delivering therapeutic genes, especially if they could be made tumour-selective. Initially, it was thought that the best course of action would be to replace tumour suppressor genes, like p53. This was followed by the trend toward using suicide genes that would convert pro-drugs [drug precursors activated on metabolism] into toxic agents, which in turn would diffuse in the tumour microenvironment and kill cells not directly infected by the virus.

In contrast, how are viruses being developed for this purpose at present?

Most recently, it has been recognised that the best utility may be to consider replicating viruses as a form of immunotherapy [encouraging the immune system to help fight cancer] and to combine them with immunoadjuvants [nonspecific stimulators of the immune system].

What are the characteristics of oncolytic viruses that make them appropriate for use in cancer treatment?

Oncolytic viruses have the ability to selectively infect and/or replicate in tumour cells, while sparing normal cells. The machinery for efficient cell killing and gene expression exists in the virus and can be easily manipulated to optimise their anti-tumour effect. They are also strong immunogens [molecules capable of inducing an immune response], and can cause immunogenic cell death in tumour cells, releasing tumour-associated antigens for processing by antigen-presenting cells.

In what ways does the environment and facilities afforded by the UPMC CancerCenter facilitate your work?

We have been able to translate our laboratory findings into the clinics very efficiently. We have wonderful laboratory facilities adjacent to our clinic and hospital, and we can transfer biologic specimens and products back and forth easily. We have significant institutional financial support to fill gaps in funding for these complex clinical trials which are never appropriately budgeted through grants. We have also been able to develop a facility for clinical grade viral production within the UPMC CancerCenter to support our efforts.
SETTING ONE’S ENEMIES against each other is a tactic typically reserved to military strategy; extending the metaphor of ‘fighting cancer’, it appears that this militaristic approach could be used for the remediation of otherwise intractable cancers. Clinicians and researchers at UPMC CancerCenter, affiliated with the University of Pittsburgh Schools of the Health Sciences, USA, are turning deadly viruses against localised tumours in an effort to help those for whom conventional strategies have failed.

Oncolytic viruses such as those developed at UPMC are characterised by their preferential infection and destruction of tumour cells. In addition to leaving healthy cells unscathed, virotherapy elicits an immune response in the host, directing endogenous defences to the oncologic frontline. It is through audacious strategies such as this that Dr David Bartlett satisfies his mission statement: “To take care of patients with advanced cancers who have run out of standard options”.

HOW IT WORKS
Oncolytic viruses are typically engineered to possess specific mutations which nullify their pathogenic potential, whilst allowing them to proliferate normally in tumour cells. Certain proteins are upregulated in tumour cells, especially those involved in cell growth and replication pathways. Viruses can be genetically manipulated to be dependent on these proteins, rendering them tumour-selective. In the case of Bartlett’s vaccinia virus, the gene encoding thymidine kinase, essential for the synthesis of nucleic acids, and thus DNA, is deleted. The resultant virus is therefore only capable of DNA synthesis, a process essential to replication, in the actively-dividing tumour cells where thymidine kinase is produced in great quantities. As the concentration of this protein is insufficient in healthy cells, the virus cannot replicate in tissues unaffected by cancer.

This tumour-specificity can be enhanced by making further mutations; deletion of the vaccinia growth factor (VGF) gene, encoding its namesake protein, for instance. VGF stimulates cell growth and division, and the production of proteins required for the virus’ sustenance. The signalling pathways on which VGF acts are often overactive in tumour cells, meaning these are the only cells in which VGF-null vaccinia virus has a chance to replicate.

Both thymidine kinase and VGF genes are deleted from the genome of Bartlett’s vaccinia virus, as these mutations were found to be most conducive to tumour-selectivity.

Physicians and scientists at the UPMC CancerCenter, USA, are genetically reprogramming viruses to eliminate solid tumours. With clinical trials underway, this novel virotherapy might someday offer hope to those who need it most.
SAFETY VS EFFICACY

Bartlett’s work represents a calculated gamble. Being a surgeon by trade, Bartlett appreciates that there’s a time and place for cautious sensitivity, and the elimination of bulky tumours is not it. Consequently, his research group elected to use the Western Reserve strain of vaccinia virus, favouring this variety over the tried-and-tested ONYX-015 and T-VEC for its superior efficiency of cell-to-cell spread. Ironic as it is, the very mechanism of cell-to-cell spread by which vaccinia virus evades the immune system and permeates tissues aids its efficacy as a cancer treatment. The vaccinia virus also refrains from entering the circulatory system, presenting the possibility of directly introducing a small dose to a tumour, leading to its pervasion of the tumour tissue without systemic toxicity.

ENHANCING THE IMMUNE RESPONSE

An inverse correlation exists between the prognosis severity of many solid cancers and the degree of tumour infiltration by immune cells. Tumour vaccines may therefore be co-administered with an oncolytic virus to augment the host immune response, thus aiding in the oncolytic effect.

Cytotoxic T lymphocytes (T cells) of the immune system eliminate all replicating vaccinia virus from the tumour in just ten days. These T cells also signal to circulating immune cells, attracting them to the tumour. Alone, targeted vaccines are able to induce the systemic circulation of tumour-specific T cells, though they are not effective at eliminating tumours. Bartlett’s team exploits the tendency of vaccinia virus to activate T cells and attract them to the tumour microenvironment to support the mechanism of tumour vaccines. By combining these synergistic therapies, both the induction and effector stages of immunity are supported.

Chemokines, proteins released by cells to attract lymphocytes to the site of infection, may also be used to enhance the recruitment of cytotoxic T cells to tumours. Bartlett’s group expressed chemokine CCL5 in the vaccinia virus (vaccinia-CCL5), finding this manipulation to enhance the attraction of lymphocytes to the tumour microenvironment, and thus the anti-tumour immune response.

Viral expression of cytokine transgenes (eg. CCL5), and some other common methods of enhancing the immunotherapeutic effects of oncolytic virus, tend to also result in impaired oncolytic activity and premature clearance of the virus from tumours. It is therefore noteworthy that Bartlett’s group found viral CCL19, another oncolytic vaccinia virus chemokine, to persist in tumours at equivalent levels to a control virus without CCL19, suggesting that oncolytic activity was not impinged upon by the chemokine. CCL19 was, however, rapidly cleared from normal tissues, potentially indicative of the therapy’s considerable tumour-selectivity, and hence safety profile.

CLINICAL POTENTIAL

Having produced a clinical grade of the Western Reserve vaccinia virus, and basic toxicology assays to ensure its safety, the therapy was submitted to clinical trial. In the first in-human phase I clinical trial, 16 patients with advanced solid tumours (including colon, breast, pancreatic and melanoma) were administered solid tumours (including colon, breast, pancreatic and melanoma) were administered an oncolytic vaccinia virus intra-tumourally. The therapy was well-tolerated, and no dose-limiting toxicities were noted. Vaccinia virus was determined to localise to cancerous tissue, and to replicate only in tumours. Indeed, evidence of vaccinia virus replication in tumours other than those injected was also observed, confirming the systemic anti-tumour activity of the novel virotherapy.

These results are very promising, though much work remains before vaccinia virus comes close to the clinical green light. As the patients enrolled in Bartlett’s phase I trial had advanced, refractory (unresponsive to treatment) tumours, complete elimination of their disease could not be fairly expected; this trial sought to demonstrate the treatment’s safety in human patients. It is during the later stages of clinical testing that the treatment’s efficacy will become clear.

Indeed, Bartlett’s oncolytic virus has the potential to succeed where others have failed. The immense virulence of vaccinia virus, and thus efficacy of its attenuated, oncolytic form, make the therapy both fast-acting and potent – properties which might allow vaccinia virus to surpass its predecessors, and make it into the clinic.

Dr David Bartlett was a senior investigator in the surgery branch at the Center for Cancer Research at the National Cancer Institute before joining the University of Pittsburgh Cancer Institute. Bartlett received his medical degree from the University of Texas Medical School at Houston, and completed his surgical training at the Hospital of the University of Pennsylvania in Philadelphia, USA.