Cancer vaccines: a clinical perspective

Using the immune system to treat cancer is an attractive proposition for patients and their doctors. It suggests low toxicity therapy, manipulating a natural process, to prevent or cure disease. Exciting advances in cancer vaccine development have recently been made.

Vaccination as a method of preventing infectious diseases has been one of the most important advances in the history of medicine. It has resulted in the eradication of smallpox and the protection of many millions of people from serious illnesses such as polio. The immune system evolved to protect animals from infection with viruses, bacteria and fungi, and using vaccination, we have enhanced the response to a number of infective agents.

As a collection of abnormal cells which replicate and may be harmful to the host, cancer can be seen to have similar attributes to infection. It seems logical that the immune system may have a role in either preventing carcinogenesis or curing established tumours. Such ideas led to the theory of cancer immunosurveillance (Dunn et al, 2002) which holds that the immune system destroys the majority of cancers before they became clinically apparent. A few nevertheless evade immunity and go on to become established tumours.

Subsequent experiments with immunodeficient mice have cast doubt on this idea except in tumours related to chronic viral infections such as lymphomas and leukaemias (Dunn et al, 2002). Of course, in patients with virus-associated immunodeficiency certain tumours such as Kaposi's sarcoma and squamous cell carcinomas are more common. In addition it was noted by William Coley as early as the 19th century that immune reactions to infection could sometimes result in simultaneous regression of tumours (Bickels et al, 2002). Furthermore spontaneous regressions are observed in tumours such as renal cancer and melanoma, in the latter case occasionally associated with autoimmune phenomena such as vitiligo (King et al, 2001).

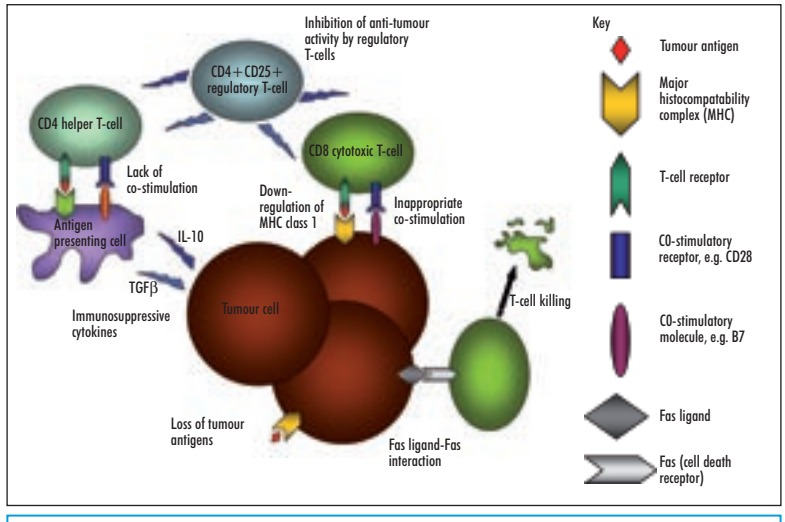
How do cancers evade the immune response?

The immune system walks a fine line between ignoring host tissue – self tolerance – and recognizing antigens or molecules associated with foreign and potentially harmful viruses or cells. There are therefore mechanisms in place to prevent the immune system activating inappropriately which may, as a consequence, allow tumour cells to evade a response. *Figure 1* summarizes some of the ways in which tumours escape the immune system. For example surface antigens and the apparatus required to present them to T-cells can be down-regulated or lost, inhibitory cytokines may be released, or regulatory T-cells which inhibit tumour cell killing may be recruited.

Are any immunological therapies currently used to treat cancer?

The field of cancer immunotherapy has seen recent success with the increase in the clinical use of immunotherapeutic agents. For some time the cytokine interleukin-2 (IL-2) has been used in the treatment of melanoma and renal cancer – trials, particularly in the latter, have demonstrated a significant clinical benefit (McDermott et al, 2005). Interferon alpha (IFNα) is used in the adjuvant treatment of melanoma, and large meta-analyses (Kirkwood et al, 2004) have shown a delay in disease recurrence and a possible survival advantage. The most exciting data of the last 2–3 years have been generated by studies of antibody therapy. The HER2 antibody trastazumab (Herceptin) is already used in HER2 positive, metastatic breast cancer and has now shown a very significant benefit in the adjuvant setting (Piccart-Gebhart et al, 2005; Romond et al, 2005). Rituximab, an antibody targetting the CD20 antigen, is used in non-Hodgkin's lymphoma (Avivi et al, 2003) and newer antibodies are effective in colorectal cancer (Venook, 2005). Currently, however, there are no cancer vaccines in use routinely outside clinical trials.

Figure 1. Mechanisms by which tumours may evade the immune system. IL-10 = interleukin-10; TGFβ = transforming growth factor-β



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What types of cancer vaccine are there?

Cancer vaccine strategies centre on stimulating an immune response to an antigen or group of antigens expressed either specifically, or to an increased level, by tumour cells. Some vaccines use whole tumour cells to provide a cocktail of target peptides. Otherwise, using knowledge gained of common tumour antigens and immunogenicity, specific peptides likely to produce anti-tumour immunity may be selected. The immune stimulation can then be enhanced by adding components such as viral vectors, costimulatory molecules or cytokines. *Table 1* summarizes some of the main vaccine types.

Vaccines may be used in two main settings, either prophylactically to prevent cancer or therapeutically to treat established disease. The latter differs from the way in which vaccines have been used in infectious disease and it is not surprising therefore that it has been difficult to develop effective agents. Work is underway to develop vaccines able to eliminate established, chronic infections such as hepatitis B (Li et al, 2005) and human immunodeficiency virus (HIV) (Slobod et al, 2005); even in these viral infections, however, there is as yet no agent in use outside clinical trials. Prophylactic cancer vaccines are more analogous to vaccines successful in infectious disease and indeed advances are being made in this area. Such a vaccine could be used to protect those at high risk of developing certain cancers such as melanoma or breast cancer, although currently the most notable work has been on hepatocellular carcinoma (HCC) and cervical cancer where carcinogenesis is directly related to viral infection.

Table 1. Main vaccine types

Vaccine	Notes
Whole-cell	Inactivated whole tumour cells. May be autologous or allogeneic
Tumour-lysate	Lysed tumour-cell lines
Shed-antigens	Captures antigens from the tumour cell surface which are more likely to be relevant immunologically
Heat-shock proteins	Involved in maturation of antigen-presenting (dendritic) cells and protein processing by cells
Peptide	Potential immunogenic subunits (epitopes) from tumour-associated antigens (TAA) selected
Recombinant viral vectors	Viral vectors carrying specially selected peptides with them may infect and activate antigen-presenting cells
Plasmid	Bacterial plasmids containing DNA coding for a tumour-associated antigen can be engineered
Virus-like particles	Mimic the structure of authentic virus particles, are recognized readily by the immune system, and present viral antigens in an authentic conformation
Anti-idiotype	Antibodies which resemble the epitope of the TAA may stimulate the same response
Dendritic cell	Dendritic cells may be primed with TAA ex-vivo to enhance antigen presentation before administration back to patient

Prophylactic cancer vaccines

The analogy between cancer and infection becomes even more relevant when it is noted that many infections actually cause cancer. Dr DM Parkin of the Clinical Trials Support Unit in Oxford presented data at the National Cancer Research Institute annual meeting in 2005. From his group's studies it is estimated that in 2002 1.9 million cases of cancer, 17.7% of the global cancer burden, were the result of infection. The main agents are:

- The bacterium *Helicobacter pylori* (5.5% of all cancer) which causes gastric malignancies
- The human papillomaviruses (HPV) (5.5%) which cause mainly skin and cervical cancers
- Hepatitis B and C (4.9%) causing HCC
- Epstein–Barr virus (1%) which causes nasopharyngeal malignancies and lymphomas
- The combination of HIV with human herpesvirus 8 (0.9%) leading to Kaposi's sarcoma.

Any vaccinations against these infections would thus have a significant effect on carcinogenesis worldwide. Hepatitis B vaccine has been available for several years. If implemented on a wider scale it has the potential to substantially reduce the incidence of HCC as demonstrated by a nationwide vaccination programme in Taiwan. Since 1984 this has reduced the incidence of HCC in children by almost half (Chang et al, 1997). More recently progress has been made in the development of a vaccine against another significant viral carcinogen, HPV.

A vaccine against cervical cancer

Cervical cancer is a sequelae of HPV infection (Lehtinen and Paavonen, 2004) and one of the most common cancers in women worldwide, with around 470 000 new cases and 230 000 deaths every year (Parkin et al, 2001). There are over 35 types of HPV with HPV-16 and HPV-18 the most common of the oncogenic varieties; a vaccine against them could prevent the majority of cervical cancers. Work published in the past 2 years shows that this may now be a reality with the development of effective, immunogenic vaccines using virus-like particles (*Table 1*).

In a study published in 2004 a randomized, placebo controlled trial was performed on 1113 women between 15 and 25 years of age in North America and Brazil (Harper et al, 2004). It confirmed 100% protection against persistent infection with HPV-16 and 18, and in the intention-to-treat analysis 92.9% protection against infection-related cytological abnormalities.

More recently, a study published in May 2005 tested a slightly different vaccine in a randomized phase II trial involving 277 young women (Villa et al, 2005). This vaccine showed high efficacy at providing protection against HPV-6 and 11 which cause genital warts as well as against the oncogenic HPV-16 and 18. Both vaccines were well tolerated and generated high titres of neutralizing serum antibody; whether this is the mechanism of

protection is unknown. Both trials provide great encouragement that a major cause of cancer mortality worldwide can be prevented. In the developed world morbidity will be avoided and money saved as abnormal cervical smear tests become less common and in developing countries, with little provision of screening, cervical cancer rates could fall dramatically. Caveats are that women would require vaccination before the age at which they become sexually active and men, in whom the vaccines have not yet been tested, should be vaccinated for herd immunity to be achieved. Duration of protection is also uncertain and the vaccine is expensive to distribute, requiring cold storage. Furthermore while HPV-16 and 18 cause most cervical cancer, other strains such as 31, 33, 35, 45 and 58 are also potentially oncogenic.

Therapeutic cancer vaccines

A more challenging target for cancer vaccines is treatment of existing tumours. In the case of the HPV vaccines discussed above, although extremely effective at preventing infection, they are not able to eliminate infection that is already established, probably because of the high numbers of replicating virus. In the setting of cancer, however, the rate of cell proliferation may not be as rapid; the major hurdle to overcome might instead be the lack of an effective cytotoxic immune response against tumour cells.

Melanoma vaccines

Melanoma is a tumour which appears to show vulnerability to attack by the immune system. Hence it is the tumour type on which the largest volume of research has been performed.

One of the techniques used to test vaccine efficacy is the tumour protection model in animals. A melanoma cell line is injected into mice with or without prior immunization with a test vaccine. Unvaccinated mice die as a result of the tumour within around 6 weeks, but immunized mice show resistance to tumour development and prolonged survival (Bystryn, 1978). This type of research provides encouragement that vaccine strategies could be successful.

To produce effective vaccines, unless whole tumour cells are used, antigens common to the tumour in different patients must be identified. In melanoma over the past 15 years several such antigens have been discovered. The first, termed 'melanoma-associated gene 1' (MAGE-1), was identified in 1991 by Boon (Traversari et al, 1992). His group used tumour-infiltrating lymphocytes to screen cDNA libraries generated from autologous melanoma vaccines. Since then many other antigens have been isolated and these are now being targeted by experimental vaccines.

Melanoma vaccines have been trialled in both the metastatic and adjuvant setting. Many studies have confirmed immune responses to the vaccine and stabilization of disease or even clinical responses. However, most studies are small and do not include a control group of patients; it is therefore difficult to separate vaccine-induced from spontaneous responses. A number of larger, randomized, controlled trials have now been carried out. One of the most studied vaccines is Melacine (Corixa Inc, Seattle) which consists of two allogeneic melanoma cell lysates combined with an immunogenic adjuvant, DETOX (detoxified Freund's adjuvant). Melacine was compared with the Dartmouth chemotherapy regimen (dacarbazine, cisplatin, carmustine and tamoxifen) in 140 patients. There was no significant difference in objective response rate (7.1% for vaccine, 10% for chemotherapy) or survival although Melacine was better tolerated (Mitchell and Von Eschen, 1997). A study involving 253 patients looking at the use of Melacine with IFNα suggested longer responses in patients receiving Melacine plus IFNα compared with IFNα alone (Mitchell, 2003). This led to a large phase III trial comparing Melacine plus IFNα in the adjuvant setting with the 'Kirkwood' high-dose IFNα regimen (Mitchell et al, 2003). After relatively short follow up there was no significant difference in outcome between the two arms although relapse-free survival was 31 months in the combination arm *vs* 25 months for high-dose IFNα.

A similar large trial was performed using a vaccine targeting the GM2 ganglioside, a cell-surface antigen, against high-dose interferon (HDI), again in the adjuvant setting (Kirkwood et al, 2001). This is the largest randomized phase III trial of a melanoma vaccine to date, recruiting 880 patients. The trial was closed early as the vaccine appeared inferior to HDI in terms of relapse-free and overall survival; conversely this has been used as evidence for the efficacy of HDI. In another large trial of 700 patients, a vaccine made from melanoma cell lysates was given to high-risk melanoma patients as adjuvant treatment. No statistical survival advantage was seen although median overall survival was 151 months in the treated compared to 88 months in the control group (Hersey et al, 2002). In summary it seems that in the adjuvant setting at least, while early phase trials suggest immune and clinical responses to vaccines, clinical benefit has been difficult to confirm in larger randomized phase III studies.

Autologous renal tumour-cell vaccines

Renal cancer is another immunologically attractive tumour as spontaneous regressions occur, and the cytokines IFNα and IL-2 are established treatments in metastatic disease. Various vaccination strategies have been used, initially including whole-cell vaccines or tumour lysates. Dendritic cell vaccines are also under study, and more recently genetically modified tumour cells have been generated with genes encoding cytokines, tumour-associated antigens or co-stimulatory molecules.

Adjuvant treatment of disease is attractive since following resection of the main tumour mass, residual disease should be minimal and any suppression of the host immune system by the primary tumour will have

been relieved. A study performed in 55 centres in Germany enrolled 558 patients with stage II and III renal cancer (Jocham et al, 2004). They were randomized to receive either no adjuvant treatment or a tumour-lysate vaccine made from 10 g of the resected tumour given as six intradermal injections at 4-week intervals. A total of 379 patients were assessable for the intention-to-treat analysis and 5-year progression-free survival rates were 68% in the controls and 77% in those vaccinated. The vaccine was well tolerated with only 12 adverse events reported. Obviously autologous vaccines are made specific to each patient, and as well as showing potential clinical benefit this trial also demonstrated that logistically it is possible to produce and administer autologous vaccines to patients attending hospitals in multiple locations.

Vaccines in other common tumour types

Aside from melanoma and renal cancer, in which a large body of work on immunological therapy has been performed, other tumours have also been targeted.

Colorectal cancer

Colorectal cancer is an obvious candidate as it remains one of the most common cancers. A number of potential vaccine targets have been identified including a group of proteins termed oncofoetal antigens. These are expressed predominantly by fetal tissue and malignancies, with limited expression by normal adult tissue. Two such antigens expressed by colorectal cancers are carcinoembryonic antigen (CEA) (Garrett and Kurtz, 1986) and 5T4 (Starzynska et al, 1992). One of the most recent CEA vaccines to be tested is CEA(6D)-TRICOM (Therion Biologics, Cambridge, MA). It uses a fowl pox or vaccinia vector containing the gene for CEA as well as three costimulatory molecules B7.1, ICAM-1, and LFA-3 (TRICOM); these three appear to synergistically stimulate T-cells.

A phase I trial, adding granulocyte-macrophage colony-stimulating factor (GM-CSF) to the vaccine, has confirmed safety and apparent efficacy (Marshall et al, 2005). Of 58 patients treated there was one complete response, 11 patients with stable or reduced CEA levels, 23 with stable disease for at least 4 months and 14 with stable disease for over 6 months. 5T4 is expressed by a number of cancer types and a vaccine, TroVax (Oxford Biomedica plc, Oxford), targeting this antigen has been produced. It uses a vaccinia-based viral vector to deliver the 5T4 gene and is being investigated in phase I and II trials (Reinis, 2004). It has demonstrated efficacy at generating T-cell and antibody responses in patients with advanced colorectal cancer and can be used alone or in combination with chemotherapy. A study currently underway at the authors' centre is using TroVax as an adjuvant treatment for patients undergoing surgical resection of liver metastases. Perhaps surprisingly chemotherapy does not demonstrate a confirmed reduction in relapse rate in this group of patients, who may have minimal residual disease, following surgery. Data from this phase II trial will be available this year.

Lung cancer

The most common malignancy in the UK and USA, lung cancer, has also been the subject of vaccine trials. A study involving 83 patients evaluated a vaccine consisting of autologous tumour cells genetically modified to secrete human GM-CSF (Nemunaitis et al, 2004). Out of 33 advanced stage patients, three demonstrated durable complete responses, two of which had bronchioalveolar carcinoma, and longer survival was seen in patients receiving vaccines secreting higher levels of GM-CSF. Another study used genetically modified cells, this time taking an allogeneic adenocarcinoma line and transfecting with the co-stimulatory molecule B7.1 (CD80) and HLA-A1 or A2 (Raez et al, 2004). A total of 19 patients with advanced metastatic disease were vaccinated intradermally every 2 weeks; up to nine doses were given. One patient had a partial response, and five had stable disease. Median survival was 18 months. Measurable CD8 responses were seen in all but one patient and toxicity was minimal.

Conclusions

An enormous body of work has now built up looking at vaccine therapy of cancer. Up until now, however, most of the work has consisted of early phase trials carried out at single centres using surrogate endpoints for efficacy such as antibody levels, the presence of specific T-cells, and in-vitro killing assays. A review looking at phase II clinical studies of cancer vaccines, performed over a 9-year period in 440 patients with metastatic cancer, reported an objective response rate of only 2.6% (Rosenberg et al, 2004).

However, what we have gained, particularly in the past 25 years, is a much greater understanding of the complexities of the immune system. We have developed a substantial knowledge base concerning the interactions between innate and adaptive immune systems and the signalling between antigen-presenting cells and T-cells. Recently the focus has turned to the nature of negative immune regulatory signals and how they can be modulated to enhance the anti-tumour response. A study by Ribas et al (2005) looked at the use of an antibody to the inhibitory T-cell receptor CTLA4 in patients with melanoma, renal cell and colon cancer. Patients exhibited autoimmune phenomena indicating breaking of immune tolerance to self-tissues, as well as anti-tumour activity in melanoma. It should now be possible to design our vaccine strategies to use this new information and so achieve greater efficacy.

The exciting work on prophylactic HPV vaccines will translate to a huge benefit in terms of morbidity and mortality from cervical cancer worldwide in the coming decades. This provides encouragement that we should perse-

vere with vaccine development to prevent other infection-related cancers and that this could evolve to vaccines which can be given prophylactically to those at high-risk of developing malignancy, or in the adjuvant setting to patients undergoing surgical resection of tumours.

Clearly a structured approach is required, with good science leading to the development of more effective vaccines which can be tested in well-designed clinical trials. Just as trials of other cancer therapies involve large, randomized, phase III clinical trials with robust clinical endpoints, so we should aim to be performing such trials of vaccines. Our patients can then benefit from the promise of well-tolerated treatments, enhancing an inherent biological process, to prevent or cure disease.

Conflict of interest: none.

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KEY POINTS

- Cancer vaccines have been shown to generate immune responses to tumours although clinical efficacy has been more difficult to prove.
- Other immune therapies such as monoclonal antibodies and cytokines are already in clinical use.
- Our understanding of the complexities of the immune system has increased dramatically in recent years.
- Prophylactic vaccination against hepatitis B reduces the risk of hepatocellular carcinoma. Human papilloma virus vaccines should reduce morbidity and mortality related to cervical cancer significantly in the next few decades.
- Manipulation of immune regulatory factors and combination with other immune therapies should improve vaccine efficacy.
- Translating recent scientific advances, through vaccine development, to phase III clinical trials could see patients benefiting in the future.